ANALYSIS OF PROGRAM ACTIVITIES
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I. INTRODUCTION

During 1954, significant advances in several important areas of cancer research and related activities were made by the National Cancer Institute and by cooperating scientists and institutions whose work it supports. Of special interest was the progress in the fields of uterine cervical cancer detection, chemotherapy, surgery, and virus-induced cancers.

The reliability of the cytological examination for the detection of uterine cervical cancer—the vaginal smear test--was conclusively demonstrated in a study of 90,000 women in Memphis and Shelby County, Tennessee over a period of more than two years. The study proved that it is possible to detect cervical cancer in its earliest stages, when the cure rate is close to 100% and that this type of cancer remains in a highly curable form for several years--long enough to permit treatment by surgery and radiation. The importance of an annual examination was thus pointed up.

Because this cytologic test is simple, inexpensive, easily applied, and accurate, it is anticipated that a nationwide attack will soon be launched on uterine cervical cancer--the second most prevalent type in women. Early diagnosis and treatment should result in a greatly reduced mortality rate.

A development of particular significance to the expanding chemotherapy program was the successful transplantation and growth of several types of human cancers in experimental animals. These transplanted human cancers may prove especially useful in screening anti-cancer compounds. Also of great interest was the confirmation, in clinical testing, of 6-mercaptopurine as one of the most effective anti-leukemic drugs yet developed.

An important advance in hormonal therapy was the treatment of breast and prostate cancers with massive doses of estrogen, a female sex hormone, which produced striking regressions in advanced cases of breast cancer accompanied by general improvement in the physical condition of the patient. In the case of prostate cancer, the effects were not as dramatic but prompt clinical improvement was frequently noted.

Indicative of the increased recognition and support given to cancer chemotherapy was the establishment of a program for the voluntary exchange of information among scientists in this field. This program was developed under the auspices of the Committee on Chemotherapy of the National Advisory Cancer Council. The American Cancer Society, The National Cancer Institute, and the Damon Runyon Memorial Fund for Cancer Research are all cooperating in this program. NCI, itself, with the opening of the Clinical Center, expanded its own chemotherapy program and increased the number of grants given for research in this field.

A review of the causes of unsuccessful results in the treatment of cancers amenable to surgical therapy showed that a large number of failures occurred because of lesion recurrences. These recurrences appeared to arise from cancer cells which seeded themselves along the edge of the incision at the time of surgery. More than 30% of the cases examined showed the presence of cancer cells in the postoperative wound. Finding a means for preventing wound seeding might increase the overall survival rate of surgically cured cancers by as much as 20 to 40 percent.

Much fundamental research was accomplished in the field of virus-induced cancer. For the first time, it became possible to isolate, purify,

and characterize the virus that caused a form of leukosis in chickens, a disease that resembles leukemia. The techniques developed will be applied to human leukemia to discover whether it, too, is caused by a virus. It was also discovered that virus-like material obtained from cell-free extracts or filtrates of leukemic mouse tissue can in some cases induce leukemias in newborn mice of certain strains and also other types of tumors.

Other activities of the National Cancer Institute, as in previous years, involved not only the support for a program of formal research by qualified investigators, but also the providing of fellowships for promising young scientists to permit them to secure advanced research training in fields related to cancer. Teaching grants were given medical and dental schools to permit improvement in the level of cancer instruction, both quantitatively and qualitatively. The States were given money on a formula basis, as well as technical assistance and guidance, for cancer control programs.

Grants were used to promote application of new knowledge to the cancer problem in the general population. These provided support for field investigations, applied and developmental research, evaluation of screening and diagnostic tests, epidemiological studies, etc.

II

INTRAMURAL ACTIVITIES

This narrative summary of research accomplishments during calendar 1954 is not all-inclusive, omitting from consideration many projects so newly instituted that valid results may not properly be discussed. Unlike previous reports, it is not organized along administrative or disciplinary lines so that some idea of a total program integrating the efforts of highly competent investigators may be presented.

Causation of Cancer

Better knowledge of factors important to the causation of cancer should ultimately lead to practical prevention of some neoplastic diseases. This has already been accomplished in those few instances where peculiarity of exposure or habit has permitted identification and elimination of hazards that increase the risk to cancer. The many agents possessing ability to evoke malignant tumors in experimental animals often have no other known common property. Their intensive study under controlled conditions in the laboratory is paralleled by studies on the etiology of cancer in man.

Sufficient correlation of experience between laboratory and clinic has been obtained to suggest that the basic principles so far discovered apply equally well to human and experimental situations, even though agreement in detail is not absolute. The cancerous response is the result of stimulation by agents, either foreign to the animal environment (extrinsic) or products of cellular metabolism (intrinsic), and heritable traits which in large measure determine the reaction of cells to their environment.

Extrinsic Agents

Chemical Compounds: Search for chemicals capable of eliciting cancers has yielded more than 600 compounds possessing carcinogenic activity. The complexion of this enterprise is changing toward search for additional agents important in the origin of clinical cancer and definition of the way in which the transformation of the normal cell to the cancerous state is accomplished by chemical agents.

Neither Dr. W. C. Hueper, nor Dr. C. H. Steffee who is collaborating with Dr. Anna Baetjer, Johns Hopkins University, has succeeded in producing cancer of the lung in experimental animals exposed to chromium and its salts. However, Dr. Hueper, during the year, did observe a few sarcomas at the site of injection of chromium or chromite ore into the pleural cavity or into bones of rats, thereby providing the first experimental evidence of carcinogenicity of these materials. Further study of the human situation will be facilitated by a new, simple, and accurate micro method for determination of chromium in biological fluids devised by Drs. C. H. Grogan and H. J. Cahnmann, although the technique does not permit determination of acid-insoluble forms of chromium.

Additional work on the causation of pulmonary cancer by Dr. C. H. Steffee attempts to reproduce in experimental animals those kinds of cancer of the lung that are important in clinical practice. He has impregnated threads with carcinogenic compounds and introduced them into the lung after a technique originally described by Dr. H. B. Andervont. Both mice and hamsters form pulmonary tumors under these circumstances, but so far rats and guinea pigs do not. Most of the neoplasms are sarcomas rather than the carcinomas desired.

Dr. Steffee has also produced tumors of the embryonic lung by a well established transplantation technique. Only one epidermoid carcinoma has been produced. Direct injection into the trachea of tars formed from condensation of cigarette smoke should be a good means of studying the ability of these materials to provoke cancer formation in the lung. The tars, however, prove to be so toxic for the mice that the dose tolerated is too small to provide a reasonable basis for estimating their carcinogenic potency. Dr. Steffee's attempts to desensitize the mice to the toxic product, presumably nicotine, have been unsuccessful.

Strong circumstantial evidence implicates 3, 4-benzpyrene as a constituent of some mixtures carcinogenic for man. Dr. H. J. Cahnmann finds this compound present in American shale oils but at lower concentration than in certain coal tars or soots. Synthetic oils are being produced by two different processes known as Bergius and Fischer-Tropsch respectively. The former, producing highly carcinogenic mixtures, is composed predominantly of aromatic compounds; the latter process yields less carcinogenic oils containing principally aliphatic compounds.

Dr. W. C. Hueper has fractionated oils made by both processes to learn more about their cancer-producing properties. The fractions range from heavy materials resembling coke through oils having lubricating properties to gasoline. The heavy fractions of Bergius products evoke neoplasms when painted on the skin of mice. The oil fractions are carcinogenic on intramuscular injection into rats. Gasoline fractions are not carcinogenic. Only the fraction of Fischer-Tropsch oil corresponding to diesel fuel elicits tumors in experimental animals. Three of 50 mice painted with the material have developed neoplasms of the skin, and no

cancers have followed intramuscular injection in rats. The carcinogenic agent involved in these experiments appears to be something other than 3, 4-benzpyrene.

The action of chemical carcinogenic agents may be modified by dietary factors. The dye, p-dimethylaminoazobenzene, produces cancer of the liver when fed to rats. Dr. A. S. Mulay reports hepatic tumors in 90 percent of male and 25 percent of female rats ingesting an adequate diet. Mere reduction of the dietary protein decreases markedly the frequency of hepatomas. Removal of the adrenal glands or administration of desoxycorticosterone abolishes the cancerous response in the liver.

The influence of organs of internal secretion on cancer formation in non-endocrine target organs is an important development and is supported by the markedly accelerated rate at which mice form tumors of the liver when treated both with female sex hormone and o-aminoazotoluene, as described by Dr. Emma Shelton.

Dr. Mulay has observed tumors of the adrenal cortex in female rats. Transplants of some of these neoplasms grow in other rats and tumor cells metastasize to the liver and lungs. Progressive growth of the transplanted adrenal tumors suppresses the growth of the adrenal bodies in the hosts, suggesting some hormone production by the cancerous cells.

Ionizing Radiations: X-rays and their component parts are powerful carcinogenic agents for man and experimental animals. A daily dose of 0.11 r of gamma rays from radium increases the frequency of leukemia and tumors of the breast in exposed mice without decreasing their life span, according to Miss Eliza Miller, Mrs. Joanne Hollcroft and Dr. C. C. Congdon. Chronic exposure to 8.8 r per day shortens the survival period of both

intact and castrated mice to about the same extent. Increased incidence of ovarian and adrenal tumors occurs among mice irradiated at birth. Their mammary glands are underdeveloped.

Dr. M. K. Deringer reports additional experiments conducted with the late Dr. Egon Lorenz on X-ray induced tumors. Exposure of hairless mice to 400 r of X-irradiation within 12 hours of birth does not increase the incidence but does decrease the average age at appearance of skin papillomas. A few cancers of the skin appear in the irradiated group. Females exposed to X-rays also develop ovarian neoplasms.

Hybrid mice exposed to total body irradiation develop more ovarian tumors than do mice that receive the same dose of x-rays directly to the exteriorized ovaries. Shielding of the ovarian region during total body X-irradiation prevents the occurrence of these tumors. Dr. Deringer's experiments imply some important indirect action of X-rays in the production of ovarian neoplasia. Support for this contention is found in recent experiments reported by Dr. H. S. Kaplan (Stanford University) and Dr. L. W. Law, both of whom found that grafts of thymic tissue from mice with high spontaneous risk to leukemia become leukemic when transplanted to suitable hybrid mice which have received total body X-irradiation. Treatment with X-rays is not essential to this type of leukemogenesis but accelerates the change, as Dr. Law has observed it to occur within one month of transplantation.

Ultraviolet Irradiations: Having established the cancer-producing power of ultraviolet rays for the skin of mice, Dr. Harold Blum is pursuing studies of the biological reactions caused by ultraviolet irradiation in an amphibian (urodele). Heavy doses to the limb cause extensive regression. The ensuing regenerative process is characterized by production of supernumerary digits or even new limbs, depending upon the area irradiated.

Regression and abnormal growth are diminished by following the ultraviolet radiation with exposure to "visible light." Members of the Department of Biology, Princeton University, are co-operating with Dr. Blum in these interesting studies.

Intrinsic Agents

Hormones: Little question exists concerning the general importance of hormones, either as naturally occurring products of cellular metabolism or synthetic compounds possessing similar or identical biological activities in the causation of cancer. The anatomical and functional integrity of certain organs depends to a large degree on hormonal stimulation. Pharmacological effects of some steroid hormones include the ability to induce tumor formation preponderantly, but not exclusively, in endocrine target organs. Dr. Roy Hertz has had extensive experience in administering drugs with female sex hormone activity for therapeutic purposes to a large number of patients. He is impressed with the comparative lack of carcinogenicity of estrogens for female genital tract even after prolonged therapy (as much as 3 years). He has observed only two cases of atypical endometrial hyperplasia. No cancers developed in the women he has studied. Apparently other factors than hormonal stimulation are important in determining the transition from normal to cancerous. This emphasizes the necessity for precise investigation of the mode of action of hormones in carcinogenesis.

Progress in this direction has been made by Dr. H. B. Andervont, who has tested the susceptibility of various inbred strains of mice and their hybrids to agents influencing the development of mammary carcinomas. Those

susceptible to induction of tumors of the breast by female sex hormones are also susceptible to the action of the agent transmitted in mother's milk which strongly influences the occurrence of mammary neoplasms in later life. The hormones and milk agent may react similarly on breast tissue, which would explain why a combination of hormonal stimulation and milk factor is most effective in producing mammary tumors. Such an intimate relationship does not exist in the susceptibility of the breast to tumors produced by chemical compounds with no estrogenic activity. An inbred strain of mice may resist the development of "spontaneous" mammary cancer but be susceptible to chemically induced tumors of the breast, and vice versa.

Excellent experimental evidence indicates no need for continuing association of the cancer cell with the agent which incited it. Some neoplasms can propagate themselves in the absence of demonstrable quantities of any known causative factor. More detailed study of developing tumors, especially those that follow some endocrine stimulus, points to an evolutionary process continuing even after cytological features are recognizable to the pathologist as cancerous. The ultimate is a cancer that will grow readily on transplantation to genetically inappropriate hosts and even in foreign species.

Some neoplasms, however, go through a period when their existence and continuing evolution depend on stimulation either of the host tissues, their own cells, or both, by the agents that caused them. An example of such dependence in testicular tumors produced by estrogenic stimulation is being studied by Dr. H. B. Andervont. Tumors of the testis are easy to detect, measure or remove. Excision of the stilbestrol pellet after a tumor

has appeared is followed either by regression of the neoplasm or its continued growth. Transplantation to other mice of tumors that continue to grow shows clearly that they are independent of the initiating stimulus. The formation of another tumor after one has regressed in the testis is accomplished rapidly by inserting another stilbestrol pellet under the skin. Some mice subsequently develop new tumors in the absence of the specific stimulus. Such observations suggest that the intensity, duration, and perhaps periodicity of the hormonal stimulus may influence the biological attributes of neoplasms as well as their histological type, frequency, and time of occurrence.

Cell-free Tissue Extracts: Dr. Ludwik Gross (Veterans Administration), in 1951, published reports of experiments in which the very low spontaneous incidence of leukemia in C3H mice was increased by the injection of cell-free extracts of leukemic tissues from AK mice. He found it necessary to inoculate the recipients within 12 hours of birth. Drs. L. W. Law and S. E. Stewart have each attempted to reproduce the experiments of Dr. Gross without success. Dr. Gross now reports that his colonies of C3H mice represent two different sublines, of which one develops leukemia much more frequently on treatment with cell-free material than does tho other. The resistant subline is the one used by NCI investigators, who are now extending their observations to include C3H mice from other sources. Dr. S. E. Stewart has employed the same injection procedure of cell-free material from leukemic tissues in hybrid mice derived from mating inbred strains with high and low expectancy of leukemia. The treated subjects developed leukemia much earlier than did the untreated control mice, but both groups developed the disease, as was expected.

Despite lack of agreement on the transmissibility of leukemia by cell-free material, all three scientists agree that injection of the same material into newborn mice is followed in an important fraction of them by the development of salivary gland (principally parotid) neoplasms of a type not previously, or at most very rarely, seen in mice. Dr. Law has also observed some subcutaneous cancers not necessarily related to the parotid lesions after injection of cell-free materials. The precise nature of these neoplasms remains to be determined. Dr. S. E. Stewart reports the frequent occurrence of tumors of the adrenal medulla in adult mice so treated within a few hours of birth.

If the cell-free extracts or filtrate ultimately prove to contain one or more filterable viruses, their biological characteristics are in some respects more similar to the action of the mammary tumor inciter than to most other known carcinogenic viruses since the cancerous response appears during adult life. One important difference has already been found, however. The progeny of mice that develop parotid tumors have not developed the lesion during three successive generations bred in Dr. Law's laboratory. These amazing advances have stimulated revewed interest in the causal relationship of filterable viruses to cancer.

A large part of the evidence needed to prove an etiologic relationship between a filterable virus and cancer rests on the ability to recover from a neoplasm a cell-free material that will induce cancer formation in another animal. Application of increasingly precise methods of quantitative biology to study of dose-response relationships of the Rous sarcoma virus in chickens by Dr. W. R. Bryan shows that failure to obtain a cell-free, carcinogenically potent extract from a neoplasm is not adequate

evidence to dismiss the possibility of a viral etiology. Dr. Bryan has produced sarcomas in chicks with varying doses of Rous virus. No virus can be recovered from many of the resulting neoplasms when the dosage produces responses in less than 50 percent of subjects even though the cancers are unequivocally caused by the agent and possess the general characteristics of such lesions. Dr. Bryan has also obtained data suggesting that dose of the inciter has some influence in determining some of the biological characteristics of Rous sarcomas. The virus-host relationship has been further defined by demonstrating changes in host susceptibility following inoculation of virus.

Dr. Herbert Kahler and Mr. B. J. Lloyd have identified the Shope fibroma virus both in extracts and tissue slices during the year. Its structural characterisitcs resemble those of the myxoma virus by electron microscopy.

The factor in milk of older mothers that protects nursing mice against future development of leukemia, previously studied by Dr. L. W. Law, is apparently not transmitted through successive generations. All old mothers do not transmit the maternal resistance factor, but milk of one high leukemic strain of mice can suppress development of leukemia in a different strain.

Genetic Influences

Heritable traits influencing the reaction of the organism to its environment are probably important in the causation of many diseases, but cancer research has been acutely aware of the major role of genetic factors in the etiology of cancer since otherwise it is difficult to obtain reproducible results from experimentation.

Further analysis of extensive data obtained by Dr. W. E. Heston on the relationship of genetic constitution to the ability of the milk agent to induce mammary cancer suggests that only one gene controls its survival. The strain of mice previously reported that gets tumors of the breast in the absence of the milk agent continues to show a 20-30 percent frequency of such lesions at an average age of 20 months. The lesions are scattered throughout the colony with no tendency to become segregated in particular family lines as have cancers of the breast arising in mice known to harbor the milk factor. Reduction of the high incidence of mammary cancers in this stock may be partly responsible for the increasing number of hepatomas now being found among the females and the appearance of ovarian, subcutaneous, reticulum cell, blood vessel and pulmonary tumors in higher than expected concentration.

Study of the localization of gene action in the control of mouse pulmonary tumor formation reveals that many tumors occur in susceptible lung tissue, whereas few occur in genetically resistant lung tissue although both were transplanted from embryos to a common adult host. The genetic control over development of this particular form of cancer is established before birth and cannot be influenced appreciably by the genetic composition of the host. Similar findings were reported in 1952 for chemical induction of pulmonary tumors, and other investigators have obtained similar evidence on the role of gene action on carcinogenesis in different organs and tissues.

An association between obesity, as determined by the lethal yellow (A^y) gene, and risk to pulmonary tumor formation was established some time ago. Since then another mouse which becomes obese because of a different

gene (Ob) has become available for study. No linkage between the Ob gene and susceptibility to pulmonary tumor has been found. Drs. W. E. Heston and M. K. Deringer find the fused tail (Fu) gene important in determining risk to tumors of the lung but not the dominant spotting (W^1) or caracul coat (Ca) genes. The list of gross characteristics determined by genetics and influencing the liability to a specific kind of neoplasm is growing.

These studies do not pertain directly to man, who does not necessarily develop the abnormalities that mice demonstrate, but such investigations permit development of highly standardized subjects as alike in their anatomical characteristics and physiological processes as peas in the same pod. The biochemist thus obtains, from study of experimental animals, sufficient reproducibility in the system to encourage his interest in defining parameters that may be assayed in human populations for their importance in determining resistance or susceptibility to certain types of cancer. Heterogeneous human populations do not lend themselves to direct approach. Their heterogeneity is probably responsible for the relative dearth of information correlating measurable physiological attributes with formation of cancer despite the numerous attempts to accomplish this desirable end.

Such research is in progress at the National Cancer Institute already. Dr. H. A. Itano, in co-operation with Dr. Linus Pauling of the California Institute of Technology, has described different types of hemoglobin and demonstrated conclusively that their production is controlled by gene action. Some of the abnormal hemoglobins are responsible for disease states. At least one appears in cancerous individuals under certain circumstances. A fourth variant, hemoglobin E, has been described during the past year.

A different type of study has been initiated by Dr. G. L. Wolff, a research fellow working with Drs. W. E. Heston and Dean Burk, who has found statistically significant differences in the rate of fermentation of glucose, in the absence of oxygen, between kidney tissue from genetically different mice. Such enterprises should be encouraged.

Genetic research has an immediately practical value as well. Various investigators interested in studying tobacco tars have inquired about the relative susceptibilities of different inbred strains of mice to induced skin tumors. Dr. H. B. Andervont reports mice of Strain I most susceptible to papilloma formation with a carcinogenic hydrocarbon, and final data on risk to epidermoid carcinoma are being prepared. This work facilitates much research on a problem important to studies of human experience.

New Tumors

Cancers of the stomach, colon, lung, and testis in experimental animals, comparable in any way to their human counterparts, have not yet been produced in sufficient number or with adequate reproducibility to serve as a reasonable basis for study of their etiology. Efforts to evoke such medically important lesions have already been cited, but another type of research seeks new tumors arising spontaneously in laboratory colonies. The occurrence of such neoplasms can often be enhanced by use of carcinogenic agents. Dr. H. L. Stewart has observed new and unusual tumors in rats during the past year and has classified the tumors arising in strain NHO mice, which include neoplasms of the nervous system and uterus, comparatively rare in other mouse lines.

Mechanism of Carcinogenesis

The way in which chemicals and other carcinogens produce cancer is important both to a better understanding of neoplasia and possibly to the design of preventive measures. Work at the NCI centers about the powerful carcinogen 2-acetylaminofluorene which produces a variety of anatomical types of cancer in rats. The compound is fed in the diet and its fate and distribution studied. Compounds chemically related to the parent material are synthesized to guide the isolation and identification of excreted metabolites and to permit assay for carcinogenic effect. Tests on 11 derivatives of compounds related to 2-acetylaminofluorene have been completed by Dr. H. P. Morris during the year. Only two produce tumors. Drs. John and Elizabeth Weisburger have identified three new urinary metabolites of 2-acetylaminofluorene and have synthesized one of them. They have also prepared the parent compound labeled with radioactive carbon. A correlation between the chemical structure of 2-acetylaminofluorene derivatives and the ability of the material to produce hepatic cancers is already suggested by the work of Dr. H. M. Dyer.

Tight union between cancer-producing agents and intracellular proteins has been proposed as a fundamental step in the production of malignant neoplasms. Some isotopically labeled 2-acetylaminofluorene does become bound to protein when fed to rats, and Dr. Dyer is able to reproduce the same phenomenon in quantitatively similar degree in isolated systems. Dr. J. White has learned from his studies of the potent hepatic carcinogen p-dimethylaminoazobenzene that this dye is first bound to protein and then degraded by cleavage of the azo linkage, a specific part of the molecule.

Nature of The Cancerous Change

Study of the first change in the transition from normal to cancerous requires systematic inquiry into the detailed structure and function of cells. It is made practical through steady technological advances and the productivity of fundamental studies in biology, biochemistry and biophysics.

Morphological Studies

Electron microscopy has revealed cytoplasm to be an extremely complex substance containing morphological entities both recognized and unknown. Isolation of the Golgi apparatus from this mixture by NCI investigators settled the question once and for all as to its existence as an entity. The work has been widely accepted. Dr. A. J. Dalton has studied a wide variety of mammalian cells during the past year. The same three basic components of the Golgi apparatus have been found in all of them, though their appearance varies in detail. He is now able to impregnate the Golgi substance selectively.

Dr. R. C. MacCardle has studied sarcoma 37 at three days after transplantation when the tumor is poorly vascularized and at six days when the tumor is well established. The earlier specimens show the Golgi material as dispersed rodlike structures and the cells as rich in calcium and magnesium, poor in iron. The cells of the fully established neoplasm have juxtanuclear networks of Golgi bodies and the concentration of iron exceeds that of calcium or magnesium.

Progress in defining subcellular structure of normal cells has been so good that it now seems profitable to intensify comparable studies of cancer cells. Dr. W. G. Banfield has recently joined the staff to prosecute this research.

Experimental Embryology

Growth of the embryo requires the formation of structurally and functionally distinct cells from a single fertilized ovum. The acquisition of specific characteristics is a function, at least in part, of interactions between cells. Dr. Clifford Grobstein has shown that formation of tubules in the primitive kidney mesenchyme can be stimulated by tissue from the embryonic central nervous system when both are grown together in tissue culture. Activity is localized in the dorsal part of the spinal cord and decreases rapidly between the 9th and 15th day of embryonal life. Similar material from spinal cords of developing chick embryos has a similar effect on primitive mouse kidney. The effect can be produced when a finely porous filter is interposed between the two tissues, but both pieces must be in contact with it. Ventral rather than dorsal spinal cord evokes the formation of cartilage in somites. The ability of nervous tissue to produce the change is limited in time, and unlike renal tubule formation does not require immediate contact between the two types of cells in culture. Cartilage induction also takes place through membrane filters. Studies of this type suggest the elaboration of chemical compounds from one tissue having profound effects on the development of other tissues. The process is in some respects the antithesis of cancer since current concepts hold that specialized cellular functions may be lost in the transition to the cancerous state, whereas embryonal cells acquired functions during development.

Attributes of the Cancerous State

The generic term, cancer, includes a wide variety of entities possessing certain common properties but exhibiting important differences as well. Such

differences may be expected to occur when cancers arise from varying cell types, but they also seem to occur in cancers having a common origin as well. The techniques involved in studying these attributes may apply equally well to elucidating the mechanism of the cancerous change. However, in the current state of their development, these techniques are better able to cope with rather large quantities of tissues than with the transition of normal to cancerous which probably affects only a few cells at a given time. Continuing search for specific biological and biochemical differences between normal and cancerous cells of similar origin may reveal new bases for approaching the treatment of cancer. The effort depends on basic studies of cell behavior in many different systems and properly forms a major segment of the intramural research effort of the National Cancer Institute.

Tissue Culture

Ability to grow cells under controlled conditions outside of the body permits observations that would be impossible otherwise. Dr. W. R. Earle and his colleagues have grown cultures of some types of cells in quantities as large as 10 - 12 grams, whereas most other methods seldom provide more than 20 - 30 milligrams. Chemically defined media for the growth of cells in culture will greatly facilitate a more precise approach to the study of cell growth. Media now available contain only a small quantity of native protein, a globulin; all the other constituents are known through the efforts of Drs. V. J. Evans, B. B. Westfall, W. R. Earle and K. K. Sanford. Ultrafiltrate of whole egg may form just as good a nutrient for proliferating cells as does chick embryo extract ultrafiltrate, and provides a less costly, more readily available material. Each type of cell has its own requirements for growth *in vitro*; each constitutes

a research problem in itself.

Drs. V. J. Evans and W. R. Earle are growing cells from human tumors that produce hormones, in collaboration with Dr. Roy Hertz. A tumor originating in islet tissue of the pancreas produced strong effects in the original patient, suggesting hypersecretion of insulin. Some insulin was detected during the early period of growth of this tumor outside of the body, but capacity to form this important hormone *in vitro* was not clearly demonstrated. A culture of hydatidiform mole, on the other hand, continues to produce chorionic gonadotrophin after many months in tissue culture even though its cells have lost their distinctive morphological characteristics.

One of the most interesting observations of the past year concerns the development of clone cultures developed by Drs. Sanford and Earle. These are grown from single cells but, as their population increases, one finds fully as wide a variation among the individuals as characterizes cultures that originate from larger initial masses of the same cell type. Tumors derived from clone cultures of the same cell type have different biological properties even though they may share common immunological characteristics.

Dr. Joseph Leighton's three-dimensional sponge matrix method of tissue culture permits tumor cells to grow in a manner similar to their usual type of growth in the body and permits identification of certain cancers of obscure origin. In addition to these obvious advantages for diagnosis, Dr. Leighton is able to study the characteristic invasive properties of malignant cells in his system. HeLa cells from a human cancer, for example, invade cells from the human uterine wall as well as cells from several embryonic tissues. The ability to study invasion represents important progress in cancer research.

Immunological Aspects

The development of diffusion chambers by Dr. G. H. Algire has afforded a means of studying reactions between tumor cells and their hosts in ways which simulate conditions of tissue culture. At the same time, they preserve the influence of the body's extracellular fluid which varies with metabolic activities of the host. Cancer cells foreign to the strain of which the individual is a member usually fail to grow in members of the strain, if they are in direct contact with host tissues. They grow well, however, when placed in diffusion chambers buried in the peritoneal cavity or in other appropriate locations. HeLa cells from human cancer survive at least 60 days in mice under these conditions. The porosity of the chamber wall is important. Foreign cells persist and grow only when cells are excluded from entering the chamber. Access of lymphocytes from host tissue destroys the foreign cancers. The importance of the lymphocytes in defense against cancer was stressed by the late Dr. James B. Murphy over 30 years ago.

Subsequent studies have associated the production of antibodies with the lymphoid apparatus. These new observations of Drs. J. L. Weaver and G. H. Algire focus attention on the importance of lymphocytes as distinct from circulating antibodies in defensive mechanisms against cancerous growth. The potential utility of conventional immunological principles in impeding cancerous growth rests on ability to demonstrate the same type of reactions in neoplasms having no characteristics foreign to their strain of origin.

This judgment may require some revision since the transplantation of normal tissue within species also has a long and discouraging history. Such experiments led to the assumption that donor and recipient must be almost as alike as identical twins in their genetic makeup. Nevertheless, Mrs. J. M.

Main and Dr. R. T. Prehn have accomplished the successful transplantation of large pieces of skin between 2 different inbred strains of mice during the year. The grafts have persisted for more than 6 months already.

Dr. M. K. Barrett has been able to grow tumors in genetically unsuitable hosts by waiting until a compatible neoplasm already growing in the mouse has reached a large size. He has also separated the factor in red blood cells responsible for inducing immunity against transplantable tumors from the iso hemaglutinins that determine blood type.

Endocrinological Studies

Protracted administration of goitrogenic compounds leads to production of tumors of the thyroid gland in rodents. Although some of these neoplasms require continued administration of the agent to develop into cancers capable of sustained growth in healthy subjects, others which are more anaplastic or malignant can grow in the absence of the agent, as shown by Dr. H. P. Morris and his group. The tumors divide themselves into those that metabolize iodine in much the same way as does normal thyroid tissue, and a larger group in which iodine-concentrating mechanisms seem to be defective. The former may concentrate a therapeutically important amount of radioactive iodine, since the dose of gamma irradiation delivered by the isotope may destroy the cancer cells.

Dr. Seymour Wollman finds that the blood radioiodide clearance by transplanted thyroid tumors involves changes in the biochemical attributes of tumor cells and can be related neither to transplantation itself nor to the quantity of iodine in the blood. Similar findings are reported by Drs. H. P. Morris and H. J. Lipner. Impairment of the iodide-concentrating mechanism

in transplanted mouse thyroid tumor is directly responsible for the inability of certain types of these neoplasms to accumulate radioactive iodine in therapeutically effective concentration. The metabolic defect in these tumors studied by Dr. Wollman is quite similar to the pharmacological effect of the thiourea compounds that were used to produce the cancers in thyroid tissue.

The speed of biological reactions is emphasized by the appearance of radioactive iodine in the colloid of the thyroid gland within 11 seconds after the administration of protein-bound iodine. The isotope appears first in the periphery but soon becomes uniformly mixed in most of the follicles. Nembutal anesthesia impedes the mixing process. The appearance of the protein-bound radioactive iodide complex in the colloid rather than in the cells offers an explanation for the observation by Dr. Wollman and Dr. Morris that thyroid tumors which contain no colloid do not accumulate radioactive iodine.

Fundamental studies of thyroid physiology by Dr. M. A. Greer have indicated the important influence of a small area in the brain stem known as the hypothalamus on thyroid function. Dr. Greer has observed the effect of transplanting the pituitary gland, which secretes a thyroid-stimulating hormone, to the eye or to the kidney in mice. These subjects continue to concentrate radioactive iodine in their thyroid glands but cannot maintain thyroid weight nor the weights of other organs known to require pituitary stimulation above those found in mice from which the pituitary glands have been completely removed (hypophysectomized). Administration of thyroxin, the principal hormone of the thyroid, stimulates uptake of radioactive iodine in these mice as it does in normal ones but produces no change in the weight of the thyroid. Certain changes occur among the cell types in the transplanted pituitaries. Dr. Greer finds that destruction of a small area in the hypothalamus inter-

feres with the thyroid-stimulating activity (thyrotrophin secretion) of the pituitary in such a way as to prevent response to goitre-producing drugs.

Discovery of new steroid hormones continues. Dr. E. M. Nadel and members of the staff of the Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts have found in guinea pig urine a new series of hormones apparently produced by the adrenals. Five of the new compounds have been crystallized; four have been identified; and the urinary excretion pattern of three has been established for animals bearing experimental tumors. These patterns seem to differ in the cancerous mice from all other experimental situations studied, except for guinea pigs receiving large amounts of total body X-irradiation. One of the steroids, 6-betahydroxycortisol, has already been recovered from human urine and serves as the first evidence for 6-betahydroxylation of the steroid nucleus in man.

Transplanted Tumors

Osteogenic sarcoma, particularly prevalent during childhood, is one of the most highly malignant forms of cancer. Dr. W. H. Eyestone is studying two forms of this disease in mice. One, metastasizing readily, forms bone in both the primary tumor and metastases, while the other which is composed predominantly of spindle-shaped cells and little bone spreads late in the course of its growth. Both of these neoplasms form more bone when growing in the extremities than in other parts of the body. Selection of the fragment for transplantation also makes a difference in the histological picture, as those pieces taken from regions of the tumor next to bone form, on subsequent growth, more bone, than do pieces taken from the periphery of the same tumors.

Dr. A. W. Hilberg has succeeded in separating a complex tumor into three of its component parts—bone, squamous epithelium, and melanomatous tissue—which grow as independent lesions.

In the course of serially transplanting a mouse melanoma into the peritoneal cavity, Dr. A. J. Dalton has noticed the appearance of a new type of cell having characteristics usually ascribed to lymphoma cells. The new cell outgrew the melanoma and eventually replaced it completely.

Malignant neoplasms produce a wide variety of effects that bring about deterioration of their hosts in many different ways. A new syndrome has been described by Dr. J. H. Edgcomb. A slowly growing cystic tumor of the skin produces large quantities of the protein, keratin, which characterizes the upper layers of epidermal cells. Death of the center of the tumor, eight to twelve weeks after it starts to grow is associated with a leukemoid reaction in which polymorphonuclear leucocytes increase tremendously in the peripheral blood. Leucocyte counts as high as 500,000 per cu. mm. have been recorded. The blood count returns to normal within 3 days after excision of this curious tumor. An elevation in the white blood cell count of much less degree accompanies the growth of many rodent neoplasms as well as some few types of human cancer. Dr. Edgcomb may have found a way of explaining this phenomenon. His work certainly suggests that a tumor may elaborate a substance with important biological activity.

Comparable reactions are not easy to find in cancer research, but the ability of a growing tumor to reduce the activity of hepatic catalase, well documented though poorly understood, is another example of a biochemical effect of a tumor on its host, which continues to be studied extensively at the

National Cancer Institute. Progress during the past year, as reported by Drs. R. E. Greenfield and V. E. Price, has revealed these significant facts:

1. An ethanol fraction of homogenized tumor tissue lowers hepatic catalase activity on intraperitoneal injection into noncancerous rats.

2. Injection of cell-free fluid from ascites tumors—cancers growing as free-living cells or small clumps in the greatly increased peritoneal fluid—has a similar effect.

3. Feeding cancerous tissue for three days will lower hepatic catalase activity to a greater extent than feeding normal tissues, suggesting that the factor resists intestinal digestion.

Correlated studies indicate that mitochondria, a form of subcellular particulate, contain most of the catalase activity in cells from liver. Hepatic catalase does not deteriorate during growth of cancer. Its total quantity is reduced.

Dr. G. H. Algire believes that localization of the strongly fluorescent dye, fluorescin, can be accomplished in different cancers through the use of drugs to diminish regional blood flow. Fluorescin has been found to be useful in localizing brain tumors during surgical operation.

The comparison of non-invasive and widely spreading forms of lymphoma, originated by Dr. Emma Shelton, has shown that neither type of neoplasm contains hyaluronidase, an enzyme which may influence the invasive quality of malignant cells.

Protein Chemistry

Proteins are the most abundant constituent of cells, other than water, and are responsible for the majority of cellular functions. Malignant tumors manufacture large quantities of protoplasm. They have no known mechanism by

which they may regulate their growth rate and share with the other organs of the body a common substrate from which they select nutrients and into which they may elaborate products of cellular metabolism. Organs and tissues form at different rates and at different times during growth of the individual. Factors responsible for such important differentials must exist. The common denominator in all such reactions is protein synthesis. Detailed knowledge of the synthetic process offers an approach to the study of cancer that probably may be exploited for prevention or cure. Some authorities argue that advances already made in the drug treatment of cancer have stemmed from information on the synthesis of nucleic acids, substances intimately related to proteins in the animal's economy.

Amino Acids: A part of the integrated program on protein chemistry at NCI is concerned with amino acids, the smallest building blocks of protein. It becomes essential to identify these materials in small quantities of tissue or body fluids. Availability of amino acids in pure forms of all isomers, as the result of earlier work of Dr. J. P. Greenstein and his colleagues, makes this practical. Mr. R. J. Koegel finds absorption spectra of various amino acids and peptides fully as characteristic and specific as melting points, permitting unambiguous identification and quantitative estimation. The problem is complicated, however, by the existence of a single amino acid in more than one form according to the spatial arrangement of its atoms (isomers).

Infrared absorption spectra of amino acids having only one asymmetric carbon atom, which permits two isomers to exist, are identical. Amino acids with two asymmetric carbon atoms, providing for four different arrangements, differ so much in infrared absorption that identification of the spatial

orientation of functional groups is possible. Study of shift in degree to which diasymmetric amino acids rotate light in aqueous and acid solutions establishes rules by which an assignment of configuration of the four isomers may be made, according to Drs. Milton Winitz, S. N. Birnbaum and J. P. Greenstein.

Mr. M. C. Otey has already recorded the rotatory dispersion of 24 different amino acids and finds it possible to determine configuration about the alpha carbon atom in amino acids with more than one asymmetric center. The configuration about the second or beta asymmetric center can be resolved by specific enzymic reactions developed by Drs. Winitz, Birnbaum and Greenstein. The chemical reactions catalyzed by enzymes are often highly specific. Of the four stereoisomers of isocitric acid, for example, only the isomer corresponding to the natural form is active when tested against an isocitric acid dehydrogenase-adenosine triphosphate system.

New amino acids continue to be discovered. During her brief visit to the National Cancer Institute, Dr. Elizabeth Work, a distinguished biochemist of University College, London, England, made studies with Dr. Greenstein of physical properties of alpha, epsilon diaminopimelic acid. Dr. Work discovered this unusual compound in bacteria in which it is a possible precursor of lysine.

Threonine, an essential amino acid, has been synthesized in an isolated biological system during the year from glycine and acetaldehyde by Dr. J. B. Gilbert.

An intimate relationship exists between carbohydrate and protein metabolism, since some compounds characteristic of each class differ by only one amino

group. This small radical when removed from an alpha amino acid forms an alpha keto acid which may be oxidized in the tricarboxylic acid cycle as is most carbohydrate; conversely, an amino group added to an alpha keto acid forms an amino acid which can enter into protein synthetic reactions. The process of transfer, called transamination, is catalyzed by different enzymes, transaminases, that require a co-enzyme.

Drs. Alton Meister, H. A. Sober and E. A. Peterson have established that pyridoxamine phosphate is a new co-enzyme for transamination. Pyridoxal phosphate has long been known to function in this manner. Ways of preventing these natural reactions are constantly being sought as a means of therapy for a wide variety of diseases, including cancer. Desoxypyridoxine phosphate, first synthesized by Drs. Peterson and Sober at the National Cancer Institute, effectively inhibits transamination *in vitro* by competing with pyridoxal or pyridoxamine phosphate. Once the inhibitor or the natural material is attached to the enzyme it cannot be displaced. Biological and possibly therapeutic effects may therefore be expected to be more pronounced among systems in which transamination proceeds at a rapid rate, according to Dr. Meister.

The alpha keto analogs of arginine, ornithine, and lysine, have been prepared during the year. The chemical methodology is materially benefited by the use of snake venom which contains large quantities of L-amino acid oxidase. The alpha keto analog of arginine cannot replace arginine in the diet of weanling rats. Either transamination does not occur or the keto acid undergoes other reactions even though transamination proceeds *in vitro*. Dr. Meister has also demonstrated the first enzymic synthesis of asparagine.

Peptides: Peptides, intermediate molecules between amino acids and proteins, are formed during protein synthesis and degradation. Availability of

pure, optically active amino acids makes it practical to pursue precise studies of these important compounds. Dr. Nobuo Izumiya, a Fulbright-Smith-Mundt fellow from Japan, and Dr. Roy Wade, University of Nottingham, England, have worked with Drs. Greenstein and Winitz and Mr. Otey on this project during the year. Synthetic peptides containing only the two optically active forms of cysteine have already been prepared.

Oxidation of L-cysteinyl-L-cysteine at pH 6.5 leads to formation of completely different L-cystinyl-L-cystine from that obtained by oxidation at pH 8.5. The reaction products of oxidation of L-cysteinyl-D-cysteine or D-cysteinyl-L-cysteine are identical at either pH 6.5 or 8.5. Such odd findings could not have been predicted and concern reversible equilibria, between sulfhydryl represented by cysteine and disulfide represented by cystine, involving proteins important to cancer because of the high rate of anaerobic metabolism in most malignant neoplasms. Intracellular proteins invariably possess free sulfhydryl groups on their surfaces and conversion to the disulfide forms will depend on the availability of oxygen in the tissues.

Drs. C. G. Baker and Leon Levintow have determined the behavior of 85 synthetic peptides in 15 different solvents for paper chromatography. This serves as a standard for examination of naturally occurring peptides in body fluids. Different methods of fractionating human blood plasma have been employed. Preliminary studies have already revealed numerous peptides present in small quantities. The concentration of free amino acids is also quite low in blood plasma, but scientists have calculated that these small amounts are adequate to account for a large part of protein synthesis in healthy rats.

Proteins: Commercially available ion exchange resins are suitable only for separating relatively small molecules, but ion exchangers made from cellulose are effective adsorbents for the chromatography of typical proteins. This real advance by Drs. H. A. Sober and E. A. Peterson, reported last year, has led to a systematic evaluation of different adsorbents for proteins. It is also possible to isolate desoxyribonucleic acids by similar techniques. Crystalline proteins homogeneous by electrophoretic and sedimentation measurements contain several components that may be affected by storage or lyophilization (drying in the frozen state).

Preliminary examination of protein fractions obtained by Drs. Peterson and Sober is in progress utilizing immunochemical techniques, with the objective of further fractionating activity. Blood serum can readily be divided into 15 to 20 components. Immune activity is maintained and fractionated. Gamma globulins can be isolated and further subdivided. Dr. J. L. Fahey is collaborating closely with Drs. Sober and Peterson and Mr. F. J. Gutter in introducing their methods into clinical investigation.

The ramifications of the technique and its unusually wide applicability exceed the ability of the National Cancer Institute to support from its own resources all of the research now clearly indicated. The originators have generously made unpublished information available to qualified scientists throughout the country in order to accelerate progress in protein chemistry.

Enzymes: Enzymic activity is really one part of protein chemistry that deals with functional aspects of protein molecules through the catalysis of chemical reactions. Drs. M. E. Maver and S. M. Birnbaum, with Drs. Peterson and Sober, have separated enzymes from co-enzymes during the year and established

new enzyme specificities.

The existence of an enzyme capable of cleaving peptide bonds involving the epsilon amino group of L-lysine was suggested by the ability of rats to grow when epsilon acetyl-L-lysine replaced the essential amino acid in the diet. Drs. Greenstein, Birnbaum and Winitz have identified the enzyme responsible as an omega-acylase. Its activity is now being determined in normal and neoplastic tissue.

Drs. Birnbaum and Winitz have completed a systematic study of the hydrolysis of amino acid esters by tissue homogenates. No specific pattern of activity having been revealed, the scientists conclude that the hydrolysis is probably accomplished by non-specific esterases.

Dr. M. E. Maver continues her studies of cathepsins from normal and cancerous tissues. Some of these important enzymes which appear to aid the rapid synthesis of protein during tumor growth have marked transpeptidase activity.

Distinctly different proteins may share common activity, as reported last year by Drs. Sober and Peterson. Drs. G. H. Hogeboom and E. L. Kuff have arrived at the same conclusion from a completely different methodological approach to the problem. Some enzymically active proteins, however, seem to exist in only one form.

Highly purified xanthine oxidase isolated by Dr. R. K. Kielley exhibits similar properties whether isolated from normal liver or hepatoma.

Nucleic Acids

Interest focuses on precursors of nucleic acids in animal tissues and their nature because some therapeutically useful agents interfere with nucleic

acid synthesis. Two large groups of these compounds called ribosenucleic (RNA) and desoxyribosenucleic (DNA) acids are intimately associated with intracellular functions and to some extent are characteristic of cytoplasm and nucleus respectively.

Dr. W. C. Schneider has found a number of desoxyribosidic compounds, precursors of DNA, in a variety of mouse and rat tissues. The concentration in mouse tumors is higher than in normal mouse tissues but is similar to the amount contained in normal rat tissues. Two compounds have been isolated from rat blood, of which one appears to be desoxycytidine.

Dr. Joseph Shack finds DNA from a single tissue to be a heterogeneous mixture of related substances varying in their susceptibility to denaturation.

Cytochemistry

Localization of intracellular function is achieved through gentle physico-chemical dissection of cells, identification of the units obtained, and determination of their chemical and biological properties. Progress made by NCI and other scientists in this difficult field has encouraged other biochemists to determine the locus of action of newly discovered enzymes within the major fractions of the cell. Much remains to be done. The "microsomal" fraction, for example, is a gross mixture, and some question regarding biochemical homogeneity of the mitochondrial fraction exists.

Research has been aided materially through the design of new instruments, with the aid of Mr. L. R. Crisp and his staff, which permit Drs. G. H. Hogeboom and E. L. Kuff to obtain reproducibly uniform and linear concentration gradients for the accurate determination of density and viscosity at any point in the

fluid column by analytical centrifugation. New sampling techniques have also been devised. Consequently, size distribution analyses have been made of cytoplasmic particulates exhibiting several different enzymatic activities and the distribution of RNA has been studied. Correlation of biochemical results with cellular structure is aided by electron microscopy carried out with Dr. A. J. Dalton.

Clinical Studies

Important though relatively non-specific changes in concentrations of plasma proteins, as measured by electrophoresis, accompany the growth of many clinical cancers. A leukemic patient has been studied at six different stages of disease activity by fractionating the plasma proteins with the new techniques devised by Drs. Peterson and Sober. Alterations in components could be correlated with the state of disease, according to Dr. J. L. Fahey. Similar studies of other cancer patients are in progress. They take a long time to complete since the cancerous state is a continuing one as far as its effects on the body are concerned. Additional projects now under way include measurements of rate of destruction and utilization of serum albumin and of the quantity of plasma proteins in the circulating blood, in absolute rather than relative terms, by Drs. J. L. Fahey and J. L. Steinfeld.

Unexplained anemia is a frequent consequence of cancerous growth. Studies on patients with leukemias and allied diseases reveal a shorter average life span of red blood cells. These findings, originally reported by Dr. Joseph Ross (Boston University), have been amply confirmed. Dr. J. L. Steinfeld is extending the investigations to a wider variety of cancers. The technique involves use of radioactive chromium as a marker. All of the 15 patients studied by Dr.

Steinfeld had active advanced cancer, and the average life span of their erythrocytes has varied from 20 to 60 days as compared with normal value of 100 - 120 days.

Metabolic balance studies contribute importantly to measurement of effects of cancer on its host by estimating net gains and net losses of such essential constituents of the body as nitrogen, minerals and vitamins. Dr. D. M. Watkin co-operates with Drs. Roy Hertz, J. L. Steinfeld, D. P. Tschudy and J. L. Fahey in a number of different studies. Two patients with carcinoma of the prostate retained calcium and protoplasmic constituents when progress of their disease was halted by effective treatment. Some leukemic patients appear to excrete more calcium than they ingest. Successful treatment of one of the three patients studied resulted in retention of calcium. Repletion of body protein stores in two patients who could not eat has been accomplished by administering food by stomach tube. Feeding them a very high protein diet has caused pronounced elevation of the blood urea nitrogen in the absence of demonstrable impairment of kidney function.

These several types of study are designed to provide objective evidence of growth or regression of cancer, since many of the cancer patients available for therapeutic study have invisible disease of undeterminable extent by direct examination. Other related projects are being initiated.

Treatment of Cancer

Surgery and radiology are effective in eradicating many clinical cancers and could be even more effective if better methods of case finding and diagnosis were available to practicing physicians. Research of this type is carried out

by other branches of the National Cancer Institute because patients available for study by the intramural research staff usually have disseminated cancers. The broad objectives, therefore, are the improvement and evaluation of surgical and radiological treatment, making use of advances in other fields of biology and medicine which offer promise of combined methods of therapy.

Substantial progress in definition of fundamental processes concerned with growth forms bases for approaching the systemic treatment of cancer with drugs. Some success in chemotherapy in turn contributes additional important data on growth mechanisms.

Surgery

Patients with advanced but relatively localized cancers of the pelvic organs or the head and neck are being admitted for complete study. Radical surgery is carried out in those cases in which the operation offers a reasonable chance of eradicating the disease. Immediate results seem encouraging, but five years must elapse before each individual case may be evaluated properly.

One of the prominent and interesting facets of the study relates to the comparatively uncommon cancers of the paranasal sinuses. Dr. R. R. Smith, with Drs. C. T. Klopp and J. M. Williams (George Washington University), has reported a new operation permitting the removal in one piece of the affected sinus and all contiguous structures, including the floor of the anterior cranial vault, frontal, maxillary, and ethmoid sinuses, orbital contents, nose, and maxilla. Several pharyngeal wall cancers have been excised with an increasingly large margin of normal tissue and the wounds closed successfully by primary restorative surgery. The main emphasis during this first year of study by

Drs. R. R. Smith and J. H. Waite has been on development of surgical procedures that allow normal physiological processes to occur following radical removal of large portions of the body.

The examination of surgical wounds for cancer cells at completion of operations designed to remove all cancer in the area has revealed contamination in 8 of 25 cases, as determined by Drs. R. R. Smith and A. W. Hilberg. Two of the patients with contaminated wounds have already developed clinical evidence of recurrent cancer, as has one additional case whose washings were negative. Additional clinical experience is required, but the imponderable factor at this point of the investigation is the currently unassessable therapeutic value of the washing procedure. Dr. Smith feels that prevention of wound seeding by cancer cells might increase the over-all survival rate of surgically cured cancers by as much as 20 to 40 percent. Correlated studies of the spread of V2 carcinoma in rabbits have been concerned with learning the characteristics of the tumor and standardizing its growth so that surgical techniques may yield reproducible and valid results.

NCI surgeons have provided their colleagues with much valuable material for study as the result of their operative procedures. They have also used their special skills to support laboratory investigations requiring surgical manipulations.

Ionizing Radiations

Treatment of cancer with X-rays at the National Cancer Institute during the past year has been on the basis of demonstrated need for this type of treatment in patients hospitalized at the Clinical Center. Delay in initiating

programmatic research in clinical roentgen-therapy has resulted from delayed installation of essential equipment, which is even now incomplete, and from difficulty in recruiting sufficient professional and specialized technical personnel because of essentially economic reasons.

Radioactive isotopes have not been introduced as therapeutic agents at the present time. Activation of appropriately designed space providing maximum protection for medical and nursing staffs who must care for the patients receiving radioactive material is expected in fiscal year 1956.

The generous gift of the Liggett and Myers Tobacco Company, a unique type of 3-million volt electrostatic generator, has just been installed. Experimental projects utilizing this valuable equipment are being initiated by Drs. H. L. Andrews and K. C. Brace.

Mrs. J. W. Hollcroft has continued her studies, commenced with the late Dr. Egon Lorenz, on the modification of radiation effects on the growth of a transplanted mouse lymphosarcoma by treating host and tumor separately with varying doses of X-rays. Daily doses for 3 days of 1000 r to the tumor and 50 r to the rest of the body are therapeutically more effective than daily doses of 1000 r to the tumor alone for 3 days. The radiosensitivity of this neoplasm is enhanced by subjecting the mice to an atmosphere of 95 percent oxygen and 5 percent carbon dioxide during treatment.

Clinical cancers often acquire resistance to the therapeutic action of X-rays even though they originally appeared to be radiosensitive. Mrs. Hollcroft has treated mice bearing transplanted lymphosarcomas with a single dose of 1000 r, which causes the tumors to shrink but then resume growth. Repetition of the X-ray dose when each neoplasm reaches the same size at which it received its first treatment generally causes the tumor cells to

become radioresistant. Some exceptions have been noted but Mrs. Hollcroft is approaching an important problem with considerable success.

Aside from improvements in technique and dosimetry, X-ray therapy of clinical cancer may be expected to gain most from a better knowledge of the basic effects produced by ionizing irradiations on cells. Research involves both direct and indirect approaches to this problem. Dr. C. R. Maxwell studies effects of X-rays on solutions of amino acids. The initial chemical effects studied thus far seem to be identical for electrons generated at 160-KV and 50-KV X-rays delivered at different dose rates. Secondary reactions vary quantitatively. Dr. A. W. Pratt finds recovery of bacteria after X-irradiation aided by depressing their metabolic rate through exposure to cold. Study of X-ray effects in yeast cells by Dr. M. M. Elkind already indicate that starvation alters their sensitivity to ionizing radiations. Total body X-irradiation of rats arrests cell division in the lining of the small intestine.

Correlated studies of morphological and chemical changes are being conducted by Dr. J. White and Dr. R. B. Williams, Naval Medical Research Institute, who find essential agreement in the results of their two different approaches to the common problem. Arrest in mitosis is paralleled by suppression of DNA synthesis. Resumption of cell division is accompanied by a threefold increase in protein, an eightfold increase in DNA synthesis. Protection of a loop of intestine by shielding against X-ray effects shows no alteration in protein or DNA metabolism in the shielded area, even though profound changes occur in an adjacent exposed loop. Perhaps studies of this type may determine successive doses of X-rays required to destroy tumors without irreparable damage to normal tissue.

X-rays have profound effects on blood vessels which in some measure also influence the response of cancers treated with ionizing radiations. Dr. R. M. Merwin has studied the effect of X-rays on the capacity of endothelium to produce new vessels. Mice were irradiated in a small area and stimuli for the growth of capillaries were applied locally within 6 hours. Doses of X-irradiation of 500 - 1500 r produce a progressive decline in the rate of revascularization in the injured area.

Rats exposed to 450 - 500 r total body irradiation develop cirrhosis of the liver when they eat a low protein diet, according to Dr. J. White. He also finds evidence suggesting that the excessive nitrogen excretion following total body irradiation reflects an increased activity of energy-yielding reactions rather than a specific effect on body protein. Dr. A. W. Pratt is studying this situation in his newly devised indirect calorimeter.

Prevention of irradiation damage is important to the treatment of cancer as well as to problems created by the introduction of nuclear fission into commercial and military life. The dramatic protection afforded by transplantation of normal homologous bone marrow against acute lethal injury has been introduced in previous reports. Dr. C. C. Congdon has clearly demonstrated protection afforded by bone as well as bone marrow in rats, mice, and guinea pigs. Rat bone also protects mice. Dose-response relationships necessary to further progress are being defined. A better source of raw material is being sought. Marrow is difficult to obtain in adequate quantities at reasonable cost, and bone presents many technical difficulties.

Intraperitoneal injection of inorganic particulate matter increases survival of mice, hamsters or guinea pigs exposed to doses of X-irradiation

that kill 50 to 90 percent of untreated animals. This phenomenon, described by Drs. W. W. Smith and F. Smith may reflect in some degree a higher resistance to bacterial infection known to be a major factor in early death from radiation injury. Survival, however, seems to be independent of capacity for antibody production but is related to the number of circulating granulocytes in the peripheral blood.

Drs. H. L. Andrews and K. C. Brace are able to suppress the hyperirritability of the central nervous system, prevent convulsions and prolong the lives of experimental animals receiving supra-lethal doses (7,500 - 15,000 r) of total body radiation. This is accomplished by anaesthetizing the subjects with pentobarbital or phenyl hydantoinate before exposure to X-rays.

Hormones

Naturally occurring and synthetic compounds possessing sex hormone activity are useful in temporarily arresting the growth of some cancers. Massive doses of estrogen may be given safely by vein or into subcutaneous tissues. The potential value of this form of therapy for advanced mammary and prostatic cancer continues to interest Dr. Roy Hertz and his colleagues, as more profound and rapid regression of breast cancers can be obtained in this manner. Prevention of undesirable side effects is achieved by providing a salt-free diet liberally supplemented with vitamins of the B complex. Estrogenic activity as determined by bioassay disappears rapidly from the blood stream.

Composite clearance data from 20 cases provide a frame of reference for the determination of hepatic, biliary and renal factors involved in clearance of estrogen from the body. Quantitative interference with biliary excretion

of bromsulphalein by the maintenance of a high blood level of estrogen, described by Dr. Hertz, may provide a means of studying the metabolism of female sex hormones by the liver and might conceivably prolong estrogenic action.

Dr. M. G. Sherer, interested in thyroid function, of which the concentration of protein-bound iodine in the plasma is considered a reliable index, confirms the observation that estrogens cause a significant rise in protein-bound iodine. This is not accompanied by an increase in the concentration of radioactive iodine by the thyroid gland. Study of the influence of estrogen on secretion rate of the thyroid has revealed no change in two patients, while the rate was reduced in another. It would seem that an increased protein-bound iodine concentration in the serum is not pathognomonic of hyperthyroidism on the basis of these observations. In addition, Dr. Sherer has shown that testosterone, metacortandracin, and metacortandrolone cause a marked fall in protein-bound iodine values and radioiodine tracer uptake by the thyroid gland.

Dr. Hertz has initiated studies of the effects of massive intravenous androgen therapy in younger patients with advanced disseminated mammary cancer in whom the dominant problem is bone pain. The procedure is well tolerated. Bioassay of the blood thus far reveals no evidence of androgenic activity.

Other clinical studies of the mechanism of sex hormones include the use of balance techniques to learn what effects estrogen and androgen may have on the body's utilization of important foodstuffs.

Correlated laboratory research by Mr. W. W. Tullner, Mr. D. B. Spencer, Dr. Silvio Bruzzone and Miss L. F. Hallman pertains to basic effects of estrogen on tissue growth and their modification by drugs. One of the first effects of estrogenic stimulation in the rat is the rapid accumulation of DNA in the nucleoli of endometrial cells. More than one nucleolus appears. Additional

studies of inhibition of estrogen-induced tissue growth by antagonists of folic acid show that the uterus of the rat may be made resistant to this inhibitory influence by prior sensitization with estrogen alone. This parallels closely experience with leukemic cells which often acquire complete resistance to antifolic compounds that originally killed large numbers of the cells.

Amphenone interferes with adrenal corticoid synthesis in the dog as well as the rat. A series of amphenone analogues have been synthesized, some of which share its biological properties. Differential studies on relative toxicity and depressant action on the central nervous system are in progress.

Mr. M. M. Graff has developed and perfected methods for determination of urinary ketosteroids and corticoids and improved a method for measurement of blood corticoid. These techniques are being used extensively in clinical investigations.

Dr. Hertz and Mr. Tullner have studied a sexually precocious 6-year-old boy during the year, who had an androgen-producing testicular neoplasm.

Additional information on the action of sex hormones in cancer is provided by Drs. Dean Burk and M. W. Woods. Most malignant tumors ferment glucose even in the presence of oxygen. Glycolytic metabolism of cancer is markedly reduced by sex hormones when studied in isolated systems. Drs. Woods and Burk have observed retardation of tumor growth on exposure of cancerous hosts to elevated environmental temperatures and decrease in glycolysis of slices taken from their tumors. Insulin overcomes the action of sex hormones on glycolysis as studied _in vitro_ but has nowhere near as great an influence on decreased fermentation resulting from temperature stress.

The same systems were studied, but slices were replaced by homogenates.

Addition of hexose diphosphate to the preparation prevents decay in the glycolytic rate, while a tiny amount of crystalline zinc insulin increases the rate of glycolysis. Drs. Burk and Woods believe that the primary reactions observed concern insulin and anti-insulin compounds that interfere with the conversion of hexose to hexose-6-phosphate. These basic concepts and methods are being applied by the same investigators to the mechanism of action of non-hormonal drugs known to retard growth of clinical and experimental cancers.

Endocrinology has contributed greatly to our knowledge of normal and neoplastic growth. Future progress requires some information on the peripheral action of hormones and would also benefit from search for other hormonally active materials in tissues. The National Cancer Institute plans to commit additional resources to these areas of research.

Other Drugs

The program developing at the National Cancer Institute is being patterned after similar therapeutic enterprises that successfully evaluated the effectiveness of chemical compounds for the treatment of malaria and bacterial infections. The best principles of pharmacology are being utilized, emphasizing objective analysis of measurable effect as the primary consideration. Not all cancer patients can co-operate in such a program, nor can experience in treating animal neoplasms be expected to predict the precise degree of activity of a compound in the clinic.

The introduction of human cancer early in the course of screening new compounds seems desirable. Some drugs may kill cancer cells selectively by virtue of their concentration in the extracellular fluid. The method originally devised at the Memorial Center by Dr. R. D. Sullivan, who will leave the

National Cancer Institute shortly, seems admirably suited to this purpose. He has injected a sufficient number of the compounds directly into a variety of superficially located cancers to suggest that physical factors are not responsible for the regressions obtained, nor can the possibility of an escharotic action be supported. Many metastases undergo no change whatever under these circumstances, while others disappear entirely. Acquisition of drug resistance has been observed on local injection just as it has followed systemic administration of chemotherapeutic agents. Absence of demonstrable effect of a potential anticancer agent does not preclude its usefulness by other routes of administration. Nevertheless, for the time being, direct screening in the clinic warrants increased emphasis as a reasonable means of selecting compounds for further work-up and study.

Some knowledge of fate and distribution of anticancer drugs is highly desirable. Determination of blood levels after administration of some chemotherapeutic agents sometimes leads to more efficient dosage schedules which improve the efficacy of therapy. Most of the anticancer agents have been active in minute quantities. Following their course in the body has not been a major effort of those who have used them, probably because of the technical difficulties in dealing with such low concentrations of substances difficult to identify by suitable chemical methods. Deprecation of others' efforts is not at all intended, but NCI investigators are incorporating this type of enterprise as a standard operating procedure wherever feasible.

Application of the basic principles may best be demonstrated by recounting experience to date with a compound with anti-riboflavin activity. The drug is incorporated into metabolically important molecules, but the

function of those molecules is impaired because the analog cannot impart the same functions to the molecule as does the natural vitamin riboflavin. Anti-riboflavin compounds suppress the growth of some experimental tumors. The one used by NCI was generously supplied by the Upjohn Company, Kalamazoo, Michigan, under the code name U-2112. The chemical structure of the drug is known, and NCI was provided with all the information available on its pharmacology and toxicity by its originators.

Despite a measurable effect on the growth of certain rodent tumors, U-2112, when given by mouth, has so far shown no notable effect on the growth of clinical cancers in the patients studied. Measurement of excretion of U-2112 in urine and feces under different conditions and determination of blood concentration has revealed that most U-2112 is probably destroyed in the alimentary canal. Only a small fraction of detectable drug gets into the blood stream, and that is excreted rapidly. No symptoms or signs of riboflavin deficiency have appeared in any of the patients treated for long periods of time. The drug does not appear to be toxic when given orally. Insufficient data are now available to permit intravenous use of U-2112. Perhaps the molecule may be modified to make it more effective. These problems will be taken up with the manufacturer. Drs. J. L. Fahey, R. D. Sullivan, J. F. Holland and Montague Lane have worked on this problem.

Another chemotherapeutic study on clinical leukemia has been completed. Childhood leukemias are usually classified as "acute," and experience indicates reasonably good correlation between therapeutic efforts in laboratory study of mice and rats and clinical investigation of acute leukemias. Dr. L. W. Law found it possible to prolong the lives of leukemic mice with two different

compounds, but combined treatment with both was more effective than the use of either one alone.

Dr. J. F. Holland decided to investigate the benefit of concurrent administration of two drugs, thought to interfere with the formation of nucleic acids, in children with acute leukemia. He chose 6-mercaptopurine and methotrexate (formerly a-methopterin), each of which has produced excellent, though temporary, remissions in the disease. Experience is limited because these leukemias are not common. It appears, nevertheless, that undesirable effects produced by this form of treatment are serious limiting factors. The series is too small to compare with results obtained by investigators at other institutions who used one or the other compound. Dr. Holland accepted a position elsewhere and Dr. C. G. Zubrod continued the study temporarily.

Dr. Abraham Goldin and associates then found the toxicity of 6-mercaptopurine and methotrexate together to be greater than either one alone in the treatment of mouse leukemia. Therapeutic effect of combined treatment equal to that provided by administration of one compound raised the cost in terms of undesirable effects. The clinicalventure is therefore being replaced by a different type of study on the treatment of leukemia.

Close co-operation between the General Medicine Branch and the Laboratory of Chemical Pharmacology is developing a highly integrated program on the chemotherapy of cancer with non-hormonal drugs, either synthetic or naturally occurring. Agents selected from a primary mouse-screening program conducted by Dr. Shear and associates are being selected for further work-up and study in both animals and man. The experimentalists are already engaged in intensive research of clinical import.

Drs. Abraham Goldin, N. O. Kaplan (Johns Hopkins University), and associates have completed a highly significant study of acetylpyridine which interferes with the synthesis of diphosphopyridine nucleotide (DPN). The latter substance, a co-enzyme, enters into many vital reactions and contains a derivative of nicotinic acid as an integral part of its molecule. The 3-acetyl pyridine replaces the nicotinamide in DPN, forming a DPN analog which functions imperfectly if at all. Injection of acetylpyridine into cancerous mice results in the formation of DPN analog in the neoplastic tissues, with a concomitant marked decrease in synthesis of true DPN. The demonstration of a co-enzyme analog through isolation and identification from the intact animal is an important milestone in the chemotherapy of cancer.

Several other groups are prosecuting metabolite-antimetabolite research as one basis for developing effective anticancer agents. One of the useful compounds produced by this type of activity is 6-mercaptopurine, referred to previously as an inhibitor of nucleic acid synthesis. The precise step in the formation of nucleic acids at which 6-mercaptopurine produces its effects appears to be at the riboside and ribotide level. Dr. Goldin, Mr. S. R. Humphreys and Mr. J. M. Venditti have shown that acute toxicity and antileukemic effect are reversed by ribotides, ribosides, and diphosphopyridine nucleotide.

Use of metabolites and antimetabolites together in treatment of cancer by Dr. Goldin and colleagues has important implications. Leukemic mice may be kept alive for extended periods of time, and a low but consistent proportion of the treated subjects do not succumb to the disease. In one experiment, for example, multiple treatments with methotrexate or aminopterin, followed by citrovorum factor, permitted half of the treated mice to live at least 65 days,

and a small fraction seem to be cured. Untreated leukemic mice used as controls were all dead in 10 to 12 days.

Work on the several hundred tumor-damaging agents discovered in the Laboratory of Chemical Pharmacology continues. Drs. J. L. Hartwell and A. W. Schrecker have prepared additional derivatives of podophyllotoxin, have isolated and identified more anticancer agents from plant sources, and have defined the spatial relationships of the atoms required for tumor-damaging potency in lignans.

Dr. Morris Belkin and associates are studying the pharmacological action of tumor-damaging substances on malignant cells from human and animal sources, using the techniques of tissue culture and histochemistry. New vital dyes developed by Dr. D. L. Vivian are aiding in clarification of long-standing obscurities in this important field. Dr. Belkin finds a delay in response of several ascites tumor cells to the administration of a nitrogen mustard compound and is characterizing nuclear change as an important index of drug effect. The objective of this project is correlation at a cellular level between physiologic behavior and structural appearance in relation to treatment.

Biochemical techniques contribute essential information on the mechanisms of action of tumor-damaging agents. Fully developed experimental cancers are studied by separating subcellular components to localize the intracellular site of action. Most of the work during the past year has dealt with podophyllotoxin and its derivatives. Drs. Joseph Leiter, V. F. Waravdekar and M. G. Kelly describe diminished utilization of glucose by treated tumors associated with marked reduction in tissue content of diphosphopyridine

nucleotide. Additional enzymic activities known to be associated with mitochondria are greatly decreased by treatment, whereas the drugs have little effect on activity of soluble enzymes. Many of the enzymes most seriously affected are concerned with the metabolism of glucose via the tricarboxylic acid cycle. Differences in distribution of ribonucleic and desoxyribonucleic acids between cellular fractions have been observed to follow treatment, though the total nitrogen content of the preparations remains constant.

Interest in tumor-damaging polysaccharides continues. Dr. M. J. Shear and staff have isolated these compounds from a variety of plant and animal tissues, including tumor. Most were inactive when tested against sarcoma 37, but some had tumor-necrotizing potency. One not only damages some forms of experimental cancer but also possesses preparative and provocative potency for the local Shwartzman reaction. Some polysaccharides have other important properties. Dr. Shear has kindly made some of these polysaccharides available to Prof. Paul Gyorgy (University of Pennsylvania) and Dr. George Springer (University of Pennsylvania and Armed Forces Graduate School of Medicine) for collaborative study of blood group activity and bifidus factor. Additional work at NCI has shown no relationship between arterial blood pressure and tumor-damaging effects. Tumor-necrotizing polysaccharides cause fever. The World Health Organization through its Expert Committee on Biological Standardization is studying the polysaccharide from S. marcescens provided by Dr. M. J. Shear and Mr. Adrian Perrault as a possible reference preparation for pyrogens. The material is being distributed to various interested institutions throughout the world. Drs. J. L. Hartwell and B. Ross have further purified and characterized chemically, polysaccharides of bacterial, plant, and animal tissue origin.

Additional work on development of drugs for clinical investigation has involved almost all members of the Laboratory of Chemical Pharmacology during the year. More compounds related to colchicine are being screened, and acute and chronic toxicity studies of colchicine derivatives, phenazines, and quinioxalines are in progress. An extract of narcissus bulbs possesses high tumor-damaging potency and low toxicity.

Filterable Viruses

Workers at the Memorial Center have published reports of temporarily beneficial effects in cancer patients who were treated with filterable viruses. Some of the agents used were themselves capable of eliciting disease, but their pathogenic qualities had generally been attenuated. Dr. M. B. Shimkin has been impressed with the quality and duration of remissions induced in the progress of human leukemia during intercurrent infection with some of the common viral diseases of childhood.

Dr. R. J. Huebner, NMI, has recently isolated viruses from the nasopharynx, APC viruses. These agents may be related to common mild respiratory illnesses. They are so specific in their growth requirements that propagation can only be obtained in the presence of human cells. The HeLa cell originated from a culture of cancer of the uterine cervix grown from a patient in Baltimore by Dr. G. O. Gey (Johns Hopkins Hospital) only a few years ago. It provides an excellent component of the substrate needed for multiplication of APC viruses in tissue culture. Dr. Huebner noted that his viruses produce severe damage to the HeLa cells and eventually kill them. Dr. R. R. Smith and Dr. Huebner are examining the possibility that a similar reaction may occur between APC viruses and cells of carcinoma of the uterine cervix in patients with that disease.

APC viruses can be divided into a number of immunologically distinct groups. Most adults so far examined at NCI possess antibodies against one or more of the viral types. Direct injection of virus into cancerous masses in the cervix produces no noteworthy effects if the patient possesses specific antibodies against the type of virus employed. Patients whose blood serum demonstrates no antibody specificity against the agent soon excavate a part of the site injected and extrude necrotic material into the vagina. This type of reaction occurs neither with the culture medium used for propagation of the virus nor with heat-killed preparations of APC viruses. The response is limited in those who show evidence of sloughing, probably because the subjects form antibodies against the strain of the agent used.

The antibody response is so rapid in some women as to suggest a type of reaction similar to that observed in patients who receive "booster" injections of tetanus toxoid some years after primary immunization. Drs. Smith and Huebner feel that the rapid antibody formation restricts the activity of the APC viruses on the cancer cells. Some means of preventing the prompt immune response is desirable and may be practical. The information already available has been achieved in an incredibly short time in view of the tremendous amount of work involved. This is a fine example of collaborative research by a virologist and a surgeon from different NIH Institutes.

Service Functions

Pathology

A large part of the achievements noted in this report has required the active participation of highly skilled professional pathologists. Members of the staff depend on them for accurate diagnosis and classification of the many lesions, both cancerous and noncancerous, that occur or are produced in animals at the NCI. The individual research accomplishments of the pathologists have been recorded in previous sections, but their anonymous contributions to this record are equally important. Drs. H. L. Stewart, T. B. Dunn and their associates have provided excellent service to the intramural research staff despite loss of personnel difficult to replace.

The Pathologic Anatomy Branch was created during the year, with Dr. H. L. Stewart as Chief, to provide tissue diagnostic and post mortem services to all the institutes who care for patients in the Clinical Center. Dr. L. B. Thomas heads the Surgical Pathology and Post Mortem Service, which has performed 76 necropsies during the year and acquired 1,100 specimens removed at surgical operation. Approximately 25 scientists at NIH now receive portions of particular organs or tissues through the Pathologic Anatomy Branch to further their research. Dr. A. W. Hilberg heads the Cytodiagnostic Service, which examines cells shed from various body orifices for the presence of cancer, or aids in investigation of drug action. At least three unsuspected carcinomas of the cervix and two unsuspected pulmonary cancers have been detected during the year, in which 1,392 specimens

were received in the laboratory and 4,921 slides were examined.

Mr. J. M. Albrecht, Head, Pathological Technology Section, and his colleagues have provided histological preparations for all investigators at NCI. Requests have required specific histochemical and enzymatic stains as well as more conventional procedures. Acquisitions totaled 103,763 pieces of tissue during the year, from which 88,549 slides were made.

Biochemical Analyses

Reference has been made previously to research accomplishments of Mr. R. J. Koegel, who is also responsible for performance of the analytical group in the Laboratory of Biochemistry. This efficient operation has conducted 5,000 individual tests for various colleagues during the year.

Equipment Repair

Finally, the small machine shop and glass blowing group in the Radiation Branch has repaired equipment cheerfully on the many occasions when breakages that required immediate action confronted members of the scientific staff.

Field Studies

The purpose of these studies is the acquisition of information relating to the cause, prevention, and control of cancer in human beings. The attack on this phase of the cancer problem has been considerably broadened and intensified during the past year with several new studies being

initiated as well as old ones being continued. At least double the number of studies are being conducted by staff members than were previously reported.

Cytological Mass Screening Test, Memphis and Shelby County, Tennessee

This continuing study of major importance indicates that cytological examination of vaginal smears obtained by aspiration is an efficient method of detecting uterine cancer. Results show that cervical carcinoma-in-situ (pre-invasive cancer of the neck of the uterus) occurs at a much earlier peak (30-34 years) than does invasive cancer, and that it remains localized for a period of more than 10 years.

Since this simple technique will detect cervical cancer in its pre-invasive stage, it should be possible by a mass screening to greatly reduce uterine cancer mortality. Because the uterus is one of the major sites of cancer in the female, it appears almost certain that this study will supply the necessary data for launching a widespread and integrated attack on this disease.

Lung Cancer

In view of the tremendous increase in lung cancer and the lack of data on the incidence rates of this disease in selected occupational groups, a number of studies have been initiated during the year.

Lung Cancer and Tobacco

A study of great popular interest is that of the association of tobacco smoking, particularly of cigarettes, with marked rise in this disease which has been observed during the past thirty years. An analysis of available data indicates that the risk of lung cancer is 10 times as great among heavy cigarette smokers as among non-cigarette smokers. To clarify

this relationship, a study, started in January 1954, is underway of 300,000 World War I veterans which will relate the cause of death to their smoking habits.

A survey of the smoking habits in a sample population is to be conducted in collaboration with the Census Bureau. Also included is a case history study on lung cancer in women.

Lung Cancer and Environmental Factors

Another study in this area, undertaken in the summer of 1954, is concerned with the occurrence of lung cancer in uranium miners of the Colorado-Utah Plateau. This project provided background data on the medical status of a group of uranium miners who will be checked repeatedly in follow-up examinations over a period of years. A related study is that of the prevalence of lung cancer among non-uranium miners in the Rocky Mountain area.

Also under way are studies of the geographic distribution of pulmonary cancer in specific areas within 15 selected States; the occurence of lung cancer and its relationship to environmental factors in selected groups of Federal civil service personnel; the increased incidence of lung, laryngeal, and bladder cancer in New Orleans; the incidence of skin and lung cancer in operating personnel of certain railroads. Most of these studies are long range and have not reached the point where the data secured will permit valid conclusions to be drawn.

In a study of cancer incidence among tobacco plant personnel, it was found that cancer of the major sites was lower than the expected number based on nationwide mortality data. This is contrary to the commonly held belief that exposure to nicotine and tobacco alkaloids may induce lung cancer.

Cancer Diagnostic or Screening Tests

An evaluation of the Penn-Dowdy, and the serum acid phosphatase tests is currently being made. The Fuchs test was studied carefully and extensively without confirmation of the claimed results. Therefore further study of this test has been discontinued.

Other studies in this area deal with the prevalence of gastric achlorhydria in selected population groups, and a study of oral and pharyngeal cancer in relation to vitamin deficiency and for the use of snuff.

Cancer Treatment

Two studies are underway in the area of cancer treatment. One is a study of survival rates in a group of treated gastric cancer patients and the other is a study of lymphoma cases treated in a New England hospital.

Miscellaneous Studies

These include studies of:

1. Cancer incidence in a group covered by a state-wide unemployment insurance.
2. Cancer incidence in selected population groups in Alabama.
3. Cancer incidence in a group exposed to abnormally high concentrations of radon gas.
4. Cancer incidence in selected occupational groups in California.
5. Environmental factors in mothers of children developing leukemia and other childhood cancers.
6. Cancer incidence among railroad workers.

7. Geographical distribution of cancer of major sites in upper New York State.

8. Identity of environmental and occupational factors which may cause cancer of the skin in a specific State.

9. Cancer incidence in several religious groups.

10. Cancer incidence in a population of 5,000 being periodically examined.

11. Cancer mortality in West Virginia.

12. Relationship of lung and bowel cancer to occupation.

Cancer Nursing

A cancer nursing study involving 49 public health agencies was completed and provided data for use in developing nursing services for cancer patients. A related activity has been a demonstration of an effective cancer nursing consultation service. To aid in the integration or improvement of cancer instruction in the basic and advanced nursing schools, a consultation service was provided on a pilot basis to schools participating in the study. Work conferences have been conducted for faculty members concerned with nursing curriculum; teaching aids have been developed; an annotated cancer nursing bibliography has been prepared. Nursing institutes have been conducted in Iowa, Tennessee, Georgia, Arizona, Oregon, Washington, Missouri, Kansas, and New York City.

III

EXTRAMURAL ACTIVITIES

The extramural program of the National Cancer Institute consists of research grants, field investigation grants, teaching grants, clinical traineeships, State aid programs, and a radium loan program. Also provided, under this program, is direct assistance as well as guidance and consultation to other Government agencies, medical schools, teaching centers, hospitals, national professional organizations, voluntary societies as well as research and other institutions. These organizations and institutions have demonstrated their interest in cancer control and their ability to carry out portions of an over-all cancer program.

Research Grants

Six hundred and sixty-nine research grants were made in 1954 to the amount of $7,552,188. Since it is impracticable to describe the accomplishments resulting from all of the currently supported projects, those selected should be considered as representative of the quality of work being done.

Initiation of Cancer (Carcinogenesis)

The agents thus far identified as cancer-causing have been chemical or physical (X-ray, etc.) in nature. They may be found in the external environment or may be products of cellular metabolism. Other agents may be the little known and little understood viruses. Individual viruses have been shown able to cause some tumors in birds, frogs, probably in fish, and in rabbits and mice. No such relationship has been evident, though suspected by some, in human tumors. The virus has been isolated and identified in the

case of the skin papilloma of rabbits. During the past year the Duke University group (Dr. Joseph Beard et. al.) which isolated the virus causing the rabbit papilloma has succeeded in isolating, purifying, and characterizing the virus that causes one form of leukosis in chickens, a disease that resembles leukemia.

In addition to the possibility that this discovery offers of developing a means for controlling a disease of great economic importance in the poultry industry, this group believes it has learned the use of techniques that can be applied to the problem of human leukemia to discover whether it, too, is caused by a virus. That this may be so is suggested by recent unconfirmed observations which seem to indicate that the leukemia in some strains of mice can be experimentally transferred from animal to animal by a virus-like agent.

Factors which modify the initiation of cancer are difficult to unravel in man and likewise may be difficult in animals. Exposure to a chemical may be followed by a latent period of years before a tumor appears in man. By that time contributing causes other than the chemical itself may be unrecognized. Thus, although workers in the chromate industry have a greater frequency of lung tumors than occurs in the general population, efforts to identify the cause and determine the mechanism of action from animal studies has been unsuccessful as yet. The lack of success may be related to failure to recognize other contributing factors. For instance, a weakly carcinogenic chemical may have its tumor-inducing properties apparently enhanced by treatment of the tissues with another chemical that is not carcinogenic alone. Such co-carcinogens have been described and are often suggested as unknown factors influencing the effects of such things as chromates

or cigarette smoke in the induction of lung cancer.

Recent work by Dr. Harold Rusch and associates at the University of Wisconsin casts some doubt on this basic concept of co-carcinogenesis since their research has shown that treatment of the skin of mice by croton oil alone will induce tumors and that croton oil is thus a carcinogen in its own right. Earlier work on which the idea of co-carcinogenesis was originally based indicated that croton oil did not cause tumors itself but speeded up and intensified the reaction to other known carcinogenic agents. It now appears that this may have been the resultant of the additive, or possibly synergistic, effect of two agents of varying carcinogenic potency.

Leads as to environmental factors that may influence the initiation of cancer in man come from the study of the rate of occurrence of different types of cancer in the races of man under similar and diverse environmental conditions. A basis for a more extended study of these factors and a clarification of the issues has been presented by Dr. Paul E. Steiner of the University of Chicago in his monograph "Cancer: Race and Geography. Some etiological, environmental, ethnological, epidemiological, and statistical aspects in Caucasoids, Mongoloids, Negroids, and Mexicans". This publication was aided by a grant from the National Cancer Institute to insure its prompt appearance and wide distribution at a cost which should place it before the eyes of medical students, practitioners, statisticians, epidemiologists, and other investigators where it can stimulate thought and generate interest in the search for etiologic agents of cancer.

Tumor Development

Once the carcinogenic change has been induced in a cell, by whatever agent and mechanism of action, the fate of the cancer cell and of the body

in which the cancer resides depends upon the success of the cancer cell, (1) in competing with normal cells for necessary growth-promoting elements, (2) in escaping from the growth-controlling factors of the host which govern normal cells, and (3) in counteracting efforts to destroy it.

A developing cancer may cause alterations in the metabolism of the host, either by its mere size or its location in a metabolically important organ, or by virtue of its own peculiar chemical appetite or metabolic products. An example of the latter is the production of abnormal serum ("Bence-Jones") proteins in patients with a relatively unusual form of tumor known as multiple myeloma. The nature and source of these unusual proteins is being actively investigated by a number of physical chemists, immunologists, and physicians. Work by Dr. Deutsch at the University of Wisconsin suggests that Bence-Jones proteins represent portions of certain normal serum protein molecules. If this is true, it raises the question as to whether the multiple myeloma cell is capable of producing only imperfect serum proteins or whether it produces larger amounts of these proteins and less of the normal serum proteins. Such peculiarities of cancer cell effects may be guides to diagnosis and to therapy.

Another phenomenon of tumor development that may also be involved in carcinogenesis is the relation of hormones to the appearance and persistence of tumors. Sex hormones have a definite and sometimes predictable effect upon tumors of the related reproductive organs. There is a complex interrelationship between effects of secretions of the pituitary body or hypophysis, the sex glands (ovary and testis), the adrenal glands, and the

thyroid, each producing hormones that affect one or more of the other endocrine glands as well as other organs of the body. The hypophysis, for example, produces a number of identifiable secretions which have a primary effect on specific organs and tissues ---, the adrenocorticotrophic hormone (ACTH), the gonadotrophic (sex-gland stimulating) hormone (FSH, LH, etc.) the thyroid-stimulating hormone (TSH), and the growth hormone.

It has recently been observed by Drs. Evans, Simpson, Moon and others at the University of California that removal of the hypophysis from rats and mice greatly reduced the number of tumors that could be induced in them by a carcinogenic chemical. When growth hormone was given to such hypophysectomized and carcinogen-treated animals, thus replacing at least one of the pituitary (hypophyseal) hormones, the frequency and rapidity of tumor appearance was enhanced. This is a further indication of the relationship of hormones to tumor growth which has been used practically in the treatment of tumors. Further mention of the therapeutic usefulness of removal or counteraction of hormones in the therapy of certain tumors will be found under the discussion of therapy.

Diagnosis

Recognition of the presence of cancer in the body can best be accomplished by direct microscopic observation of cells removed from the tumor or from body fluids into which they have been shed. Presence of a cancer may also be suspected from X-ray shadows of the tumor itself or of alterations of normal X-ray appearances of body structures through the replacement of normal tissue by cancer cells. These methods may not be adequate to reveal small or deep-seated cancer, however. In a few such instances, peculiar effects of the cancer cells on body constituents may

reveal their presence, as in the case of the Bence-Jones serum proteins in multiple myeloma.

An active search for similar abnormalities of blood, urine, feces, gastric secretion, etc. is being pressed in many places. Immunochemical differences in the blood serum proteins under normal and neoplastic conditions have been reported by Dr. I. A. Parfentjev at Yale University. From a study of more than 2,000 sera he has been able to create two sets of criteria- - one for separating normal from pathological sera, and the other for separating sera of cancer patients from sera with an abnormal protein pattern not associated with cancer. In patients with active malignancy, he found an increase in the total globulin concentration which, with certain qualifications, is consistent.

Therapy

Treatment of cancer is currently attempted by surgery, radiation, and drugs, alone or in combination. Continual progress has been made in all of these modes as research has developed new knowledge and techniques for destroying malignant tissue; for preserving the life of the patient while radical treatment is being given, and for rehabilitating the patient to as nearly a normal and productive life as possible. Improved methods of anaesthesia, replacement of blood by transfusion of whole blood or essential blood components, antibiotics to combat infection, restoration to normal levels of essential constituents of tissue fluids, control of nutrition, and other measures have made possible extensive surgery of cancers once thought inoperable.

More careful determination of tumor radiation dose and the use of higher energy radiation sources (electrostatic generators, linear electron

accelerators, betatrons, radioactive isotopes, etc.) have improved the treatment of tumors by radiation. Inhibition of tumor growth and, in some cases, temporary or apparently permanent disappearance of primary and metastatic tumors have been accomplished by surgical or radiological destruction of sources of tumor-stimulating hormones.

Elimination of sex glands, of the adrenal cortex, and of the hypophysis or pituitary body have favorably influenced the regression of cancers of the prostate, breast and of some other organs. Destruction of the pituitary by surgery is often incomplete and the patient is subjected to surgical hazard. Destruction by radiation has been accomplished with the newer high energy beams, but this also may be incomplete and at the same time cause damage to important adjacent normal structures. To avoid these complications, Dr. Theodore Rasmussen, formerly at the University of Chicago, has used the surgical approach to place a number of radioactive yttrium pellets in the hypophysis. By appropriately positioning these pellets to give intense local irradiation with beta particles that are not highly penetrating, he has been able to determine the location and radiation dosage necessary to produce complete destruction of the human pituitary body without significant damage to the brain, adjacent nerves, and other structures .

Much of the surgical and radiological therapy of cancer is only palliative, but there is an increasing percentage of "five year cures" in many of the types of cancers treated by these methods alone or together. An interesting phenomenon has been observed, however, in some patients who have survived treatment for more than five years without evidence of malignant disease. They eventually exhibit a recurrence of cancer of the

original type. This capacity of some malignant cells to remain unnoticed and apparently quiescent for many years only to make themselves evident and deadly much later presents an interesting problem for further study. It is reminiscent of the situation in tumor development in which there may be a long latent period between the exposure to an adequately carcinogenic agent and the appearance of a palpable tumor.

There has long been an argument as to whether surgery or radiation is the treatment of choice for cancer of the uterine cervix. Now it has been discovered by Dr. and Mrs. Graham at the Vincent Memorial Hospital in Boston that it may be possible to predict which patients will respond better to radiation and which might better be referred for surgery because they are not likely to respond to radiation. Following a small dose of radiation to the tumor, cytological studies of cells from the patient's vagina show different reactions in different patients. Correlation of these observations with the subsequent course of the patients, whether treated by surgery or radiation, makes the Grahams believe they can determine the treatment of choice. This hypothesis is being intensively investigated.

Treatment of cancer by drugs or chemotherapy has long been attempted without very much success that could be reproduced. An occasional dramatic response of temporary nature has often given unwarranted encouragement to wishful thinkers. Even longer term improvement reported as following drug therapy has been questioned. Did the patient have cancer, or was it a case of spontaneous remission? Careful studies are in progress on the natural history of untreated and treated human cancer of various types and sites to serve as a baseline for evaluation of the effects of chemical agents and natural products. Intensive work is under way on the

synthesis and selection of new compounds, on their toxicity, on the criteria for evaluation of their effects on various types of human cancer, and on the mechanism of their action. Rapid exchange of information on progress in this field is being facilitated by issuance of a bulletin on current research in cancer chemotherapy, by informal and formal conferences, by preparation of a bibliography on the subject, and by integration of the results in a central registry and the publication of reviews.

Research on the synthesis of steroid hormones, their metabolic effects, their alteration in the body, and their control of tumor growth has pointed the way to improved methods for palliative management of disseminated inoperable cancer, especially of the breast, prostate, ovaries, testes.

Additional human trials have demonstrated the effectiveness of nitrogen mustard, folic acid antagonists (aminopterin, amethopterin, etc.) triethylene melamine (TEM), triethylene phosphoramide (TEPA) and its related sulfur compound (Thio-TEPA), and myeleran against an occasional solid tumor and more frequently against one or another form of leukemia or lymphoma. Compounds derived from microorganisms, such as azaserine and puromycin, offer promise as alternatives to other agents or in combination with them. Clinical trials of 6-mercaptopurine (6-MP) as initial therapy for acute leukemia or after other agents have lost their effectiveness have shown that remissions of varying duration are obtained in about 40 percent of the patients. Other studies suggest that 6-MP given in combination with other agents such as azaserine or cortisone may have an enhanced effect.

It has been discovered by Dr. John Kidd at Cornell University Medical College that a small amount of normal guinea pig serum injected into the abdominal cavity of a mouse bearing a well-established transplanted

lymphosarcoma will cause prompt destruction of the tumor cells and disappearance of the tumor. The untreated tumor-bearing control mice were quickly killed by their tumors. The peculiar property of guinea pig serum has not been found in the sera of any other animal species although many have been tested. The guinea pig serum was found to be more specific and more effective than treatment with radiation or chemical agents. Efforts are in progress to identify the specific component(s) of guinea pig serum responsible for this phenomenon and to find out whether means can be devised to demonstrate the effect against other types of transplanted and spontaneous tumors. These observations may point the way to new avenues of research in tumor therapy.

It is difficult to study human tumors biochemically or with chemotherapeutic agents because of their variability from patient to patient and the short time that they are avilable in good condition. Investigators at Boston University, Sloan-Kettering Institute, University of Virginia, and at the Children's Cancer Research Foundation have found that, by pretreatment of hamsters and rats with cortisone and/or irradiation, it is possible to transplant some human tumors and to secure their continuous growth in the first transplant host and in other recipient transplant generations. Although most of the human tumors so transplanted have not grown, there are now several types of transplantable tumors of human origin growing rapidly on a mass production process. Large quantities of tumor tissue are available for extensive biochemical and chemotherapeutic studies. It remains to be seen whether a human tumor grown in a hamster or rat retains its human character. If so it may be especially useful in screening for compounds effective in cancer therapy.

Analysis of 1954 Research Grants

An examination of the research interests of scientists participating in the National Cancer Institute's research grants program is made every year. An analysis of the 1954 program shows that, based on the number of grants, Carcinogenesis remains the major area of interest followed by Tumor Development and Clinical studies. The most popular subject was Tissue Synthesis.

In terms of dollars invested, Clinical studies have received the greatest percentage of money spent. This results from the sharp increase in funds allotted for chemotherapy research.

The following table shows the breakdown of 1954 research grants by areas of interest.

1954 NCI Research Grants

Area	Funds Allotted	Percent of Total Funds	Number of Grants	Percent of Total Grants
Carcinogenesis	$2,389,644	31.7%	250	37.4%
External Stimuli	625,301	8.3	72 1/2	10.8
Internal Stimuli	887,241	11.8	84	12.6
Mechanisms	877,102	11.6	93 1/2	14.0
Tumor Development	$2,280,725	30.2%	226 2/3	33.9%
Tissue Synthesis	1,405,614	18.6	154 2/3	23.1
Host-Tumor Relations	875,111	11.6	72	10.8
Clinical	$2,567,147	38.1%	161 1/3	24.1%
Epidemiology	38,859	0.5	6	0.9
Diagnosis	404,291	5.4	45 1/3	6.8
Therapy	2,123,997	28.1	110	16.4
Other	$ 314,672	4.1%	31	4.6%
Total	$7,552,188	100.0%	669	100.0%

Teaching Grants

Grants under this program have been maintained at the same levels - $25,000 for each 4-year medical and osteopathic school, and $5,000 for each 2-year medical and dental school. During 1954, 82 medical, 42 dental, and 6 osteopathic schools participated in this program. July 1, 1954 marked the seventh anniversary of this activity and an over-all review of the program at that time indicated without question that these grants throughout the years have been instrumental in improving the cancer instruction provided under-graduate students in these professional schools.

Clinical Traineeships

As in the past, continued efforts have been made to increase the reservoir of trained physicians competent to manage the cancer case. During the year 160 trainees were supported in 71 institutions throughout the country. A review of the activities of past trainees, accomplished this year, indicates that the great majority of physicians receiving this training have continued to be active in some phase of the cancer field.

Field Investigation Grants

This program provides support on a project basis for field investigations, applied and developmental research, community studies, and surveys and pilot projects. All of these activities contribute to methods for the prevention, control, diagnosis, and treatment of cancer. The program has been continued at the same financial level as previously, but projects of better quality and type have been stimulated. A number of significant accomplishments have been reported during the past year by grantees receiving support under this program.

One of these accomplishments is the development of a simple screening procedure to detect gastric achlorhydria by means of a modified tubeless gastric analysis (Segal). This gives promise of potential aid in attacking the difficult problem of early discovery of gastric cancer. Another involves the completion of the first step in the instrumentation phase of the remote fluoroscopic control of Roentgen therapy (Morgan). Results of this project will contribute to improved cancer therapy.

Yet another development is the discovery that the portal of entry of benzidine and other amines is directly through the intact skin (Meigs). This finding is important in the concept that metabolites of benzidine are a factor in the causation of bladder cancer. A grantee (Kotin) has demonstrated the presence of carcinogenic substances in the atmosphere as air pollutants originating from engine exhausts and industrial processes. This study has indicated a possible association between air pollutants and pulmonary carcinogenesis in man.

A research grantee has demonstrated that a large proportion of malignant tumors are multicentric in origin (McGrath); a finding which will have considerable significance in cancer therapy. Another grantee (Grinberg) has shown that the incidence rate for corpus cancer in the Jewish population in Israel is the same as in the Non-Jewish population of the United States, but the incidence of cervical cancer is definitely less. These data offer practical leads in developing information on the etiology of human cancer.

Data on nitrogen balance and the influence of steroid and hormone therapy which may be of great practical importance in the nutritional care

and rehabilitation of cancer patients have been provided by a grantee (Elman). Grant funds have been used to obtain significant data bearing on the mechanism of speech in post laryngectomized patients (DiCarlo). These data are of major significance in the rehabilitation of these individuals. The search for cancer diagnostic tests has been continued by a number of grantees without encouraging results, although several new tests have been reported during the year.

State Aid Program

The grant funds distributed under this program on a formula basis to State and territorial health agencies to establish cancer control programs have remained at the same level as the previous year. This situation has been a deterrent to expansion in the over-all activities supported. Although a few States have redirected the use of their funds, by and large, their programs have remained the same or been reduced in scope due to the curtailment of funds for this purpose and the lack of qualified personnel within the States. As a consequence the consultation services provided by this branch to official health agencies have been somewhat decreased during 1954.

Radium Loan Program

This program has continued as in previous years with radium being provided on loan on an annual contract basis to 54 hospitals with qualified radiologists located in 30 States, including the District of Columbia. While many newer modalities have been developed for cancer radiotherapy, there are still a large number of requests for loans under this program. In fact, throughout the year there has been practically no radium on hand available for distribution.

IV

INFORMATION AND PUBLICATIONS

The public health aspect of cancer requires, in addition to the exchange of information among scientists, that knowledge gained through research be communicated promptly and continually to both the medical profession and the lay public with the object of reducing mortality through control of the disease in the population. Data from laboratory research, and the findings of epidemiological and statistical studies useful to physicians, medical educators, public health and hospital administrators, and the public in general, are disseminated through reports, publications, exhibits, films, articles in professional journals and lay magazines, and through cooperation with science writers and others seeking information on which to base articles or reports for distribution through public media. Among the most important of these activities is the preparation of regular and special reports on research progress and related activities of the National Cancer Institute as required by the Congress and the Executive Branch of the Government.

Reports

Regular required annual reports were prepared on the work of the Institute, one for the 12 month period ending December 31, 1953, and another for the Surgeon General's annual report for fiscal year 1954. Other regular or recurring reports prepared included:

Three quarterly reports on progress in intramural and extramural research and other activities for the Director, NIH; 34 weekly reports

(beginning in April) on developments in intramural and extramural research and other program elements, as well as on activities of Institute staff members in connection with their respective programs; reports of progress in seven areas of research for the information, primarily, of the Congress, and a statement in support of the 1956 budget for the Director's use before House and Senate committees on appropriations.

Preparation of non-recurring reports included: A special report on research progress in 1953 for inclusion in testimony of the Director before the Appropriations Committees of the Congress; a special report on the status of the NCI Integrated Chemotherapy Program; and a special report on publications co-sponsored by NCI during the last five years.

Also prepared were: An extensive compilation of developments in cancer research, on a nationwide basis for the past 5 years, for a report to be published by the Albert and Mary Lasker Foundation; and a special report on the cancer control program of the National Cancer Institute through technical assistance to the States, in response to a request from the Medical Services Task Force of the Hoover Commission.

Others prepared included: A supplementary budget statement covering fields of research and related activities worthy of special emphasis, for the Director; excerpts from the Congressional hearings on the 1954-55 budgets, and from the Health Inquiry hearings of the House Interstate and Foreign Commerce Committee (October 1953); and a statement giving information on the Journal of the National Cancer Institute and justification for its continued publication, in support of a request for approval of this periodical by the Bureau of the Budget.

Two special reports by Dr. Kaiser, one on the cancer teaching program in medical schools, the other on the cancer teaching program in dental schools, were edited and revised, and submitted to Public Health Reports.

Publications

A new directory, "Cancer Services and Facilities in the United States, 1954," was compiled and sent to the Government Printing Office with a first order for 10,000 copies. This will replace the 1950 edition. "Meeting the Challenge," a supplement to the book, "The Challenge of Cancer," published in 1950, was written and sent to press. New copy was prepared and photographs were selected for a printed brochure on the Institute. This will replace the present mimeographed NCI brochure.

Preparation was begun of the first issue of "Current Research in Cancer Chemotherapy," which was expected to be ready early in 1955. It will be issued from time to time to facilitate the exchange of information between investigators engaged in cancer chemotherapy research. This is part of a program sponsored by the National Advisory Cancer Council through its Committee on Chemotherapy, with the cooperation of the National Cancer Institute, the American Cancer Society, and the Damon Runyon Memorial Fund.

The summary report, "Morbidity from Cancer in the United States - Variation in Incidence by Age, Sex, Race, Marital Status, and Geography," was prepared editorially and forwarded for printing as a Public Health Monograph. This comprises the first part of a summary of the 10-city cancer morbidity studies made by the National Cancer Institute.

Speeches, Articles, Releases to the Press

Seven articles- five for professional magazines, two for lay publications - and ten speeches were prepared for presentation or publication. Several of the Director's speeches were requested for publication by editors of professional journals. Pictures in connection with articles were provided as requested. Eleven releases to the press, professional journals, and science writers, as well as seven press summaries of scientific papers scheduled for presentation, were prepared and distributed.

Clearance of Non-Research Papers

Clearance of non-research papers and speeches by NCI staff members continued, in conformance with Service and Department policies and procedures. Thirty-nine speeches and papers by Institute scientists were cleared during the year for either presentation or publication, or both.

Exhibits

An NCI unit was designed as part of an NIH exhibit on "Recent Developments in Medical Research" and shown at a Health Fair for the lay public during the annual clinical session of the American Medical Association in Miami, Florida, in December. The exhibit, "Half of All Cancer Involves Sites Accessible to Direct Examination," (for professional audiences) was booked for nine showings; the environmental respiratory cancer exhibit for three showings. A new exhibit for lay audiences was designed, which will show the magnitude of the cancer problem, principal research approaches, and clinically useful products of research.

Films

The sixth and last film in the professional diagnostic series, entitled "Lung Cancer: The Problem of Early Diagnosis," was released, a joint project of the Institute and the American Cancer Society. All six films in this series, and "Breast Self-Examination" were shown, through arrangements with the State Department, at the VI International Cancer Congress in Sao Paulo, Brazil.

Slides

Forty new slides were produced during the year, most of them dealing with cancer statistics, and 28 Clinical Center slides were acquired. Other slides, including 44 on oral cancer, 8 or breast prosthesis, as well as laboratory and historical slides, were supplied as requested for speeches and lectures by NCI staff members.

Radio - TV Educational Project

Letters were sent to approximately 1,000 college and university teachers of radio and television courses and to program directors of university and educational radio and TV stations offering a kit of cancer informational materials for classroom and workshop use. Seventy requests were received, with additional replies indicating interest in receiving the materials during the coming academic year.

Public Inquiries

Public inquiries handled during the year approximated 1,700, requiring 538 individual letter replies, 510 form letter replies, 594 telephone calls, and distribution of over 3,750 pieces of informational literature. Requests for information were received from the White House,

Congressmen, and various Government agencies; medical and pre-medical students, nurses, doctors, and all levels of students from elementary to college and post-graduate.

Distribution

The two-volume publication of Proceedings of the Second National Cancer Conference, held in Cincinnati in 1952, was received from the American Cancer Society and distributed to State Health Departments, regional medical directors, members of the National Advisory Cancer Council, the Cancer Control Committee, U.S.P.H.S. Hospitals, cancer coordinators, medical libraries, and selected cancer hospitals. Bulk mailings of other publications were made, varying in number and type of addressees, for a year's total of 15,000 copies.

Service to the Press

Science writers and reporters regularly call for information in connection with news or feature stories, or for statements or comments on cancer news developments.

Interviews with Institute staff members were arranged for science writers or reporters representing the following professional or lay magazines and newspapers or wire services: Science News Letter, Town Journal, New York Times, Scripps-Howard News Service, Newspaper Enterprise Association, and the Times-Herald, Post, and Evening Star Papers of Washington, D. C.

Assistance was given to more than a dozen writers in developing stories for their magazines or news services including those from the Saturday Evening Post and United Press.

Assistance was given staff members of the Columbia Broadcasting System in making motion picture footage of Dr. Heller and Dr. Hueper for use on a future program in the "See It Now" television series.

Journal of the National Cancer Institute

Six issues of the bi-monthly Journal of the National Cancer Institute were published during the year. With the December issue were published the proceedings of a symposium on "Twenty-five Years of Progress in Mammalian Genetics and Cancer," which was conducted at the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, June 27 to 30. During the year 174 manuscripts were submitted for the Journal, including 63 by NCI authors and 111 by outside authors. Of these, 123 were accepted for publication, including 50 by NCI authors and 73 by outside authors. The total of 174 manuscripts submitted for the Journal compares with 123 submitted in 1953, 126 in 1952, 117 in 1951, and 112 in 1950. In view of the limited publication outlets for scientific papers, the steadily increasing number of manuscripts submitted for the Journal of the National Cancer Institute which should be published has lead to serious consideration of the advisability of recommending that the Journal be either enlarged or placed on a monthly schedule.

Circulation of the Journal totaled 1,477 copies in 1954, including 582 paid subscriptions, and 895 free subscriptions of which 662 were domestic and 233 foreign. The total circulation in 1953 was 1,407.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of Director
LABORATORY OR BRANCH

3\.
SECTION OR SERVICE

4\.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-001
SERIAL NO

6. Administration of National Cancer Institute
PROJECT TITLE

7. Dr. J. R. Heller
PRINCIPAL INVESTIGATOR(S)

8. Dr. G. Seger and Mr. J. M. Hannan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Participate in the determination of policies governing the National Institutes of Health; direct the over-all administration of the National Cancer Institute in accordance with these policies; coordinate Institute programs with those of other Federal and non-governmental organizations; provide the internal administrative services of the Institute.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCI-001
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$51,675	3	6	9	3	6	9	
FY 1956	$51,675	3	6	9	3	6	9	

12. BUDGET ACTIVITY

RESEARCH ☐ ADMINISTRATION ☒

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

NONE

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-001
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954

NONE

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Office Services Section
SECTION OR SERVICE

4. LOCATION (IF OTHER THAN BETHESDA)

5. NCI-002
SERIAL NO.

6. Variety of administrative management functions in connection with operation of the Institute
PROJECT TITLE

7. Gladys P. Gulick
PRINCIPAL INVESTIGATOR (S)

8. Celeste Vasco & Lola Byrnes (unit supervisors)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

1. Develops working procedures in areas of travel, overtime, time and leave; prepares special reports; maintains control of equipment on loan; reviews & approves requisitions for supplies, services, printing, shipping.

2. Processes papers on all types of personnel actions such as recruitment, promotion, transfer, reassignment and termination for Civil Service & Commissioned personnel, visiting scientists, consultants and contractors.

3. Provides centralized travel services for the NCI which include domestic, foreign and meeting travel; travel in connection with Council and committee members; preparation of vouchers, control of funds, preparation of reports, etc. In this connection, 738 orders; 52 cancellations and 856 vouchers (686 regular vouchers & 170 fiscal vouchers) were prepared during 1954.

4. Provides a central records unit for maintenance and control of records. (See attached report of unit). In addition, files patterned on those in the Director's Office were set up in the Endocrinology, General Medicine and Radiation Branches and the files in the Office of the Associate Director in Charge of Research were revised in accordance with regulations which require the retirement of records every three years.

5. Provides a typing pool to absorb overflow from all branches and to cover offices in absence of regular personnel. Part of the work accomplished by this unit was the typing and/or retyping of 93 manuscripts with an average of 31 pages each. These were also proofread.

6. Provides duplicating services for entire Institute with special emphasis on the grants program. Personnel in this unit man tape recorders, or projectors as necessary for meetings within the Institute.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-002
Serial No.

Operation of Mail & Records Unit Calendar Year 1954

	No. of Pieces
Incoming Mail:	
Total Received & Routed	70,980
Reviewed for Routing	51,312
Reviewed & Previous Correspondence Pulled	52,956
Recorded	60
Outgoing Mail:	
Total Dispatched	194,268
Correspondence Reviewed	121,800
Records:	
Charged-out	8,388
Classified	41,304
Filed	62,460
Indexed	14,208
Requests for:	
Information	2,388
Records	8,436
Total Man Hours	9,324

PROJECT REPORT FORM (Cont'd)

0. NCI-002
SERIAL NO.

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1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$72,325 1/		13	13		13	13	
FY 1956	$72,325 1/		13	13		13	13	

1/ Includes $20,000 for telephone service at Bethesda for entire Institute.

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2. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☒

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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3. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

NONE

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4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE

15. NCI-002
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office ~~of~~ the ~~Associate~~ Director ~~in Charge of Research~~
LABORATORY OR BRANCH

3. Office Services Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5 NCI-003
SERIAL NO

6. Variety of administrative management functions in connection with operation of the research area of the Institute.
PROJECT TITLE

7. Gladys P. Gulick
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Prepares travel orders, itineraries, vouchers; prepares overtime reports; types manuscripts and letters and files reports and correspondence.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

Page 2

PROJECT REPORT FORM (Cont'd)

10. NCI-003
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$31,605		6	6	–	6	6	
FY 1956	$31,908		6	6	–	6	6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for 15, 16, 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. ~~Editorial Office~~ Office of the Director
LABORATORY OR BRANCH

3. NCI Journal
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-004
SERIAL NO.

6. Publication of 6 bimonthly issues of the Journal of the National Cancer Institute
PROJECT TITLE

7. Doris M. Chaney, Managing Editor
PRINCIPAL INVESTIGATOR(S)

8. Isabel K. Neely and Joan P. Cochran, Editorial Assistants
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Two major activities are carried out:

1) Clearance of all research manuscripts by NCI staff for publication wherever specified by author.

2) Publication of the Journal of the National Cancer Institute.

Specifically: 1) Manage (for the Board of Editors) review of all manuscripts for publication. Prepare correspondence to authors, editors and reviewers concerning these manuscripts and maintain detailed records.

2) Edit all manuscripts for publication in JNCI, mark manuscripts for printer, proofread galley and page proof, order and distribute reprints, manage production of Journal, prepare correspondence to printer, authors, and general public, and maintain free distribution lists and files.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

Page 2

PROJECT REPORT FORM (Cont'd)

10. NCI-004
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$25,132	1	3	4	1	3	4	
FY 1956	$29,186	2	2	4	2	2	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

None

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15-16-17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda, Maryland
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-005(a)
SERIAL NO.

6. Annual Reports
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Miss Marshino, Mr. Callahan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the preparation of an annual report, as required by the DHEW.

The annual report was prepared on the work of the Institute for the period July 1, 1952 to December 31, 1953. This 18-month period included Fiscal Year 1953 and the last 6 months of calendar year 1953, thereby putting the Annual Report on a calendar year basis instead of a Fiscal Year basis as heretofore. Reports were received from the Office of the Associate Director in charge of Research, Biometry and Epidemiology Branch, Field Investigations and Demonstrations Branch, and the Research Grants Branch. From these, along with the annual report of the Cancer Reports Section, a 79-page document covering significant progress of intramural and extramural research, field studies, and other related activities and services, was prepared and submitted to Scientific Reports Branch, NIH. This report is intended for intramural use only.

From the above report, a shorter, condensed version was prepared for inclusion in the printed annual report of the Public Health Service.

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION

PROJECT REPORT FORM (Cont'd)

10. NCI-005(c)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4863	3	1	4	1/3	1/3	2/3	None
FY 1956	$4865	3	1	4	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda, Maryland
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-005(b)
SERIAL NO.

6. Quarterly and semi-annual reports
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Callahan, Miss Gegan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

These activities provide for the preparation of (1) a report at the close of each quarter year on progress in intramural and extramural research and other activities, and (2) a semi-annual report on papers published in outside journals by staff members, and abstracts of these papers.

Three quarterly reports were prepared for the Director, NIH.

The semi-annual report on papers published in outside journals by NCI staff members, and abstracts of these papers, were compiled and prepared for the first half of the year. This report was dincontinued thereafter as the information was requested on project forms as a part of the annual report.

The quarterly report is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-005(c)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,863	2	1	3	1/3	1/3	2/3	None
FY 1956	$4,865	2	1	3	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-005(c)
SERIAL NO.

6. Weekly reports
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Callahan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to provide, to the Director, NIH, on a weekly basis, brief accounts of items of interest concerning activities of Institute staff members in connection with their respective programs, as well as reports of important developments in intramural and extramural research and other program elements.

Responsibility for preparation of the weekly report series was assigned to the Cancer Reports Section in April 1954. During the remainder of the year 34 reports were prepared. Of these, 30 contained a total of 90 items, and 4 were negative.

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCI-085(c)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,863	2	1	3	1/3	1/3	2/3	None
FY 1956	$4,865	2	1	3	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-005(d)
SERIAL NO.

6. Research Progress Reports
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Barney, Mr. Callahan, Mrs. Mizen
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to make available to the Congress regular information on intramural and extramural research progress. Reports are prepared monthly, based on information supplied by various Institute investigators.

During the year, research progress reports were prepared and submitted to Scientific Reports Branch, NIH, on the following subjects:

"The Problem of Leukemia"
"Supervoltage X-ray for Cancer Diagnosis"
"Uterine Cancer and the Cytology Test"
"Transparent Chamber Technique in Cancer Research"
"Growing and Studying Cells Outside the Body: The Tissue Culture Technique"
"Viruses and Cancer"
"The Effect of Hormones on Cancer"

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCI- 005 (d)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 7973	4	1	5	2/3	1/3	1	None
FY 1956	$ 11,048	5	1	6	1	1/3	1 1/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-005(a)
SERIAL NC

6. Special reports, statements
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Barney, Mr. Callahan, Mrs. Mizen, Miss Drayer
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the preparation of non-recurring reports or statements as requested by members of Congress, Dr. Sebrell or members of his staff, or the Director, NCI.

Information for these reports is compiled and prepared in the Section. Several types of reports prepared during the year were:

A special report on intramural and extramural research progress in the calendar year 1953 for inclusion in testimony of Dr. Heller for the Labor-Health, Education and Welfare subcommittee of the Committee on Appropriations; a special report on the status of the NCI Integrated Chemotherapy Program, for use by Dr. Shannon, Associate Director, NIH; a special report on publications co-sponsored by NCI during the last five years.

Also prepared were: a voluminous compilation of developments in cancer research on a nation-wide basis for the past 5 years, as requested by Mrs. Mary L. Lasker, to be published by the Albert and Mary Lasker Foundation under the tentative titale, "What Progress in Cancer Research?"; a special report on the cancer control program of the National Cancer Institute through technical assistance to the States, in response to a request from the Medical Services Task Force of the Hoover Commission.

Also prepared were: A supplementary budget statement covering fields of research and related activities worthy of special amphasis, for Dr. Heller; three special statements on research accomplishments of NCI grantees in New England; excerpts from the Congressional hearings on the 1954-55 budgets, and from the

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-005(e)
SERIAL NO.

Continuation of
Page 1

Health Inquiry Hearings of the Wolverton Committee (October 1953); a statement giving information on the Journal of the National Cancer Institute and justification for its continued publication, in support of requests for approval of this periodical by the Bureau of the Budget, as required by DHEW regulations.

Two special reports by Dr. Kaiser, one on the cancer teaching program in medical schools, the other on the cancer teaching program in dental schools, were edited, processed, and submitted to Public Health Reports.

These special reports and statements provide essential information to specific requests on various aspects of cancer research which come, for the most part, from members of Congress.

This activity is expected to continue on an irregular basis.

10. NCI-005(C)
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7973	5	2	7	2/3	1/3	1	None
FY 1956	$7956	5	2	7	2/3	1/3	1	None

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-006(a)
SERIAL NO

6. Monograph, "Morbidity from Cancer in the United States - Variation in Incidence by Age, Sex, Race, Marital Status, and Geography."
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Miss Bain, Miss Gegan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the editorial preparation and clearance of the monograph, "Morbidity from Cancer In the United States--Variation in Incidence by Age, Sex, Race, Marital Status, and Geography."

This document of 122 pages, written in the Biometry and Epidemiology Branch, was forwarded for printing as a Public Health Monograph. It comprises the first part of a summary of the 10-city Cancer Morbidity Survey, and provides data on cancer incidence, prevalence, and mortality in the United States.

It is planned to print 3,000 copies of this monograph, 1,000 of which will be distributed to National health organizations, State and local health officers, and other professional personnel engaged in cancer work. The remaining 2,000 copies will be bound together with a second monograph on the cancer morbidity studies to be published later.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI- 0c6(a)
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4863	1	3	4	1/3	1/3	2/3	None
FY 1956	$4865	1	3	4	1/3	1/3	2/3	None

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-006 (F)
SERIAL NO

6. Cancer Services and Facilities
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Miss Marshino, Mrs. Mizen, Miss Bain
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for a new directory, "Cancer Services and Facilities in the United States, 1954," which will replace the 1950 edition. A first order has been placed with the Government Printing Office for 10,000 copies. The directory is intended to serve cancer control program planners and administrators, personnel concerned with securing services for the cancer patient, students in the welfare, medical and allied fields, and citizens who may be concerned with the cancer problem.

The directory, compiled entirely in this Section from correspondence with State health officials, contains basic cancer statistics, a summary of State legislation on cancer, lists of tissue diagnostic services, cyto-diagnostic services, cancer clinics, cancer hospitals, home nursing services, hospitals providimg home medical care service, State-supported cancer diagnostic and treatment services, and other related services and facilities.

It is proposed to reissue this directory approximately every five years, or as the information therein becomes out of date.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCt 006(f)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7,973	3	3	6	2/3	1/3	1	None
FY 1956	0	0	0	0	0	0	0	

12. BUDGET ACTIVITY:

RESEARCH ☒
ADMINISTRATION ☐
REVIEW & APPROVAL ☐
TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-006(c)
SERIAL NO

6. Exchange of information on current progress in cancer chemotherapy
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Kassack, Mrs. Wall, Mrs. Layton
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the issuance, on an irregular basis, of "Current Research in Cancer Chemotherapy," to provide investigators engaged in cancer chemotherapy with an exchange of information on the development and evaluation of chemotherapeutic agents.

The total program, of which this is one phase, is sponsored by the National Advisory Cancer Council with the cooperation of the National Cancer Institute, the American Cancer Society, and the Damon Runyon Fund. Letters were sent to all scientists interested in cancer chemotherapy, inviting them to join with other investigators in this exchange of information. Three hundred letters were sent out in November and by the year's end, 200 had replied favorably. Questionnaires were then sent to this group requesting information on staffs, facilities, and programs devoted to work in cancer chemotherapy.

As the year closed, plans were completed for the first issue of "Current Research in Cancer Chemotherapy." This will provide a means of exchange of informal reports on fields of activity, work in progress, and other items of mutual interest that investigators may wish to volunteer.

This project will provide the Committee on Chemotherapy of the National Advisory Cancer Council with information indicating the extent and nature of cancer chemotherapy research both here and abroad and should be of value in determining the type of expansion needed.

This activity will continue on an irregular basis.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCl-006(c)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4863	3	1	4	1/3	1/3	2/3	None
FY 1956	$4,865	3	1	4	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-006(d)
SERIAL NO

6. "Meeting the Challenge"
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Barney
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to bring up to date the book "The Challenge of Cancer," (by Lester Grant, published in 1950) by adding a supplement describing recent developments in the various aspects of cancer research.

The supplement, entitled "Meeting the Challenge," was prepared in the Section, cleared, and submitted to GPO for printing. It contains a bibliography and is divided into 5 parts: Cancer Research in the United States, Diagnosis of Cancer, Treatment of Cancer, Chemotherapy of Cancer, and Epidemiology of Cancer.

The supplement, to be printed in the same size and format as the earlier publication, will be distributed with that publication on an individual basis.

No additional work on this activity is anticipated in the coming year.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCr 006(d)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$3,108	2	1	3	1/3	0	1/3	None
FY 1956	0	0	0	0	0	0	0	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-006(2)
SERIAL NO

6. National Cancer Institute brochure
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Callahan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to prepare a brochure, for printing, which will describe the National Cancer Institute and all its activities, both intramural and extramural, its place in the national attack on cancer, the magnitude of the cancer problem, and which will contain photographs selected from both intramural and extramural activities.

Copy for this publication has been prepared and photographs have been selected.

This printed brochure will replace the present mimeographed NCI Brochure and will be distributed to the lay public as requested for information on the Institute. Many such requests are received in the Section from the general public. Preparation of the brochure has proceeded with a long-term value in mind; no statistical data are used which would be changed by new findings.

The brochure will be completed and submitted to GPO during the coming year. Distribution of this publication will continue until such time as revision is considered necessary.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-006(e)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$3108	2	1	3	1/3	0	1/3	None
FY 1956	$4865	2	1	3	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-006(7)
SERIAL NO

6. Distribution of Publications
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mrs. Wall, Mrs. Layton
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the bulk distribution of publications on various aspects of cancer research and related activities produced either by the Institute or in cooperation with other Federal or State agencies.

Mailing lists include: State and local health officers; professional organizations; professional schools -- medical, dental, public health, and public health nursing; tumor clinics; cancer societies (U.S. and foreign), and health educators in both the United States and overseas.

The Proceedings of the Second National Cancer Conference, held in Cincinnati in 1952, were distributed during the year to: the Surgeon General's offices and the bureaus downtown, Dr. Sebrell and his staff at NIH, branch chiefs and section heads of NCI, and to cancer coordinators, State Health Departments, regional medical directors, members of the National Advisory Cancer Council, the Cancer Control Committee, U.S.P.H.S. hospitals, medical libraries, and selected cancer hospitals.

Other bulk mailings were made, varying in number and type of addressees, for a year's total of 15,000 copies.

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-016 (2)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,863	2	1	3	1/3	1/3	2/3	None
FY 1956	$4865	2	1	3	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-007
SERIAL NO

6. Exhibits, films, slides
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mrs. Wall, Mrs. Layton
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the production and distribution of audio-visual materials on the various aspects of Institute research for professional audiences.

EXHIBITS-An NCI exhibit was designed as part of an NIH exhibit on "Recent Developments in Medical Research" for showing at a Health Fair for the lay public during the annual clinical session of the American Medical Association in Miami, Florida in November. The exhibit, "Half of All Cancer Involves Sites Accessible to Direct Examination" (for professional audiences) was booked for 9 showings; the environmental respiratory cancer exhibit for 3 showings. A new exhibit was designed for lay audiences which will show the magnitude of the cancer problem, principal research approaches, and clinically useful products of research.

FILMS-The sixth and last film in the professional diagnostic series, entitled "Lung Cancer: The Problem of Early Diagnosis," was released in November, a joint project of the Institute and the American Cancer Society. Our six films in this series, and "Breast Self-Examination" were shown, through arrangements with the State Department, at the VI International Cancer Congress in Sao Paulo, Brazil, in July. "Challenge: Science Against Cancer" continues to be very popular in schools. Two additional prints were purchased for Institute use and 2 for the New York Regional Office.

SLIDES-Forty new slides were produced during the year, most of them dealing with cancer statistics, and 28 Clinical Center slides were acquired. Other slides, including 44 on oral cancer, 8 on breast prothesis, as well as laboratory and historical slides, were supplied as requested for speeches and lectures by NCI staff members.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCI-007
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,863	2	1	3	1/3	1/3	2/3	None
FY 1956	$4,865	2	1	3	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

no entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-208(a)
SERIAL NO

6. Speeches, articles, releases to the press
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Barney, Mr. Callahan, Mrs. Mizen, Miss Drayer
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides the medical profession and its various segments, and the public in general, with information on the program of the National Cancer Institute, developments in basic scientific research, epidemiological investigations, and the constant application of laboratory findings and clinical experience to the cancer problem at the level of the patient.

This is accomplished through the preparation and/or editing and clearance of news releases, speeches, magazine articles and manuscripts for both the lay and professional press.

During the year 10 speeches and 7 articles - five of the latter for professional magazines and 2 for lay publications - were prepared for presentation or publication. Several of the Director's speeches were requested for publication by editors of professional journals. Still pictures in connection with articles were provided as requested. Eleven releases to the press, professional journals and science writers, and 7 press summaries of scientific papers scheduled for presentation, were prepared and distributed.

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCI-008 (I)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7973	5	3	8	2/3	1/3	1	None
FY 1956	$11,048	6	3	9	1	1/3	1 1/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5 NQ-008(C-
SERIAL NO

6. Statement of the Director, NCI, before House and Senate hearings on appropriations.
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Dr. Light
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

This activity provides for the preparation of a statement in support of the Institute budget for fiscal year 1956 for the Director's use before House and Senate hearings on appropriations.

This statement includes comments on the major accomplishments of the Institute, and areas of work contemplated during the coming year. Supplementary materials are prepared as requested. These may include special fields of research or related activities worthy of special emphasis, as well as any visual aid materials deemed appropriate to the presentation.

This is a recurring activity for the Section.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCI-0084
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4863	2	1	3	1/3	1/3	2/3	None
FY 1956	$4865	2	1	3	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-OD 8(c)
SERIAL NO

6. Clearance of Non-research papers
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Callahan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the clearance of non-research papers and speeches by NCI staff members, in conformance with Service and Department policies and procedures.

Papers or speeches submitted to the Section for clearance are read in the Section for editorial accuracy, style of presentation, clarity, and conformance to policy. Appropriate reviewers are chosen, either in the Institute or in other divisions of the Public Health Service where the area of work is representative of that discussed in the paper or speech. Inter-bureau clearance, if necessary, proceeds concurrently with NCI clearance. The number of reviewers varies depending upon the subject matter and the scope of the discussion. Comments of reviewers, if any, are transmitted direct to the author but are not identified as to source. The author is asked to incorporate comments into the manuscript or state his reasons for rejecting them. This correspondence is then submitted to the Director, NCI, on whose approval the item is forwarded for completion of clearance through the Scientific Reports Branch, NIH. Notification of final clearance is sent to the author through his Branch Chief.

During the year, 39 speeches and papers were processed through the Cancer Reports Section for either presentation or publication, or both.

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NC1-008(c)
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 4,863	2	1	3	1/3	1/3	2/3	None
FY 1956	$ 4,865	2	1	3	1/3	1/3	2/3	None

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-008(d)
SERIAL NO

6. NCI guest lecture by Dr. Charles B. Huggins
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Barney
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provided for the completion of plans and all arrangements for the NCI lecture in the NIH Guest Lecture series, by Dr. Charles B. Huggins of Chicago, on "The Endocrinology of Mammary Cancer."

Work included the preparation, arrangements for printing, and mailing of the announcement; writing and mailing of letters of invitation, and preparation of a news release.

This is a recurring activity for the Section.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NH-068(d)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4863	2	1	3	1/3	1/3	2/3	None
FY 1956	$4865	2	1	3	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-005(w)
SERIAL NO

6. Reference collection
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Miss Bain
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to circulate journals, periodicals, press releases and other materials to the staff of the Cancer Reports Section and professional staff members of the Institute, and to maintain reference files of these materials for use as needed by writers of the Section and other Institute staff members.

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-008(e)
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$1,755	1	1	2	0	1/3	1/3	None
FY 1956	$ 1,773	1	1	2	0	1/3	1/3	None

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI 009
SERIAL NO

6. Radio-TV educational project
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Miss Drayer
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to provide kits of cancer informational materials to college and university teachers of radio and television courses and to program directors of university and educational radio and TV stations for classroom and workshop use.

With approval of the Office of Education for the general plan, form letters offering our kit of informational materials on cancer were sent to about 1,000 college and university teachers of radio and television courses and to program directors of university and educational radio and TV stations.

Close to 70 requests were received, with additional replies indicating interest in receiving the materials during the coming academic year, since our offering letter was sent close to the end of most of the schools' spring semester.

This will be a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-009
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4863	2	2	4	1/3	1/3	2/3	None
FY 1956	$4865	2	2	4	1/3	1/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5 NCI-010
SERIAL NO

6. Public Inquiries
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Miss Speicher
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the handling and reply of day-to-day inquiries from the general public.

Inquiries handled during the year approximated 1,700, requiring 538 individual letter replies, 510 form letter replies, 594 telephone calls, and distribution of over 3,750 pieces of informational literature. Requests for information were received from Congressmen, the White House, and various [redacted] Government agencies; medical and pre-medical students, nurses, doctors, and all levels of students from elementary to college and post-graduate.

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-010
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$3,510	1	1	2	0	2/3	2/3	None
FY 1956	$3545	1	1	2	0	2/3	2/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Office of the Director
LABORATORY OR BRANCH

3. Cancer Reports Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-011
SERIAL NO

6. Service to the press and other media
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Barney, Mr. Callahan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to accomodate science writers or reporters who regularly call the Section for information in developing news or feature stories, or for statements or comments of staff members relative to a particular development or story on cancer research.

During the year interviews with Institute staff members were arranged for science writers or reporters representing the following professional or lay magazines and newspapers or wire services:

Science News Letter, Town Journal, New York Times, Scripps-Howard News Service, Newspaper Enterprise Association, and the Times-Herald, Post, and Evening Star papers of Washington, D. C.

Assistance was given to more than a dozen writers in developing stories for their magazines or news services including those from the Saturday Evening Post, and United Press.

Assistance was given staff members of the Columbia Broadcasting System in making motion picture footage of Dr. Heller and Dr. Hueper for use on a future program in the "See It Now" television series.

This is a continuing activity.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-011
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$3,108	3	1	4	1/3	0	1/3	None
FY 1956	$3,092	3	1	4	1/3	0	1/3	None

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

National Cancer Institute
INSTITUTE

2. Research Grants & Fellowships Branch
LABORATORY OR BRANCH

SECTION OR SERVICE

4. LOCATION (IF OTHER THAN BETHESDA)

5. NCI-025
SERIAL NO.

Administration of cancer research grants program.
PROJECT TITLE

R. G. Meader
PRINCIPAL INVESTIGATOR(S)

C. D. Larsen, H. F. Seversmith, A. Weissler
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: To encourage, promote, and support basic and applied research in non-Federal institutions leading toward delineation of the causes, nature, and methods of diagnosis, therapy and prevention of cancer.

Methods: A. Preparation of awards in the name of the Surgeon General of grants for research in fields pertinent to the problem of neoplastic growth, upon recommendation of the National Advisory Cancer Council.

B. Conduct of surveys and analyses of the field of cancer research and of the research supported through cancer research grants to evaluate the extent to which all promising leads are being explored and to indicate areas in which current efforts might profitably be expanded or new efforts be initiated.

C. Exploration of new methods and techniques of administration by which the objectives might be more fully accomplished.

D. Consultation with investigators to acquaint them with the opportunities for support of expansion of their current research efforts and of development of new approaches also to inform them of related or pertinent studies by others so their work can progress more rapidly through rapid exchange of information or through collaboration; also to aid them in administrative problems related to their research grants.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

. PROJECT DESCRIPTION (Continued)

E. Dissemination of information on research in fields related to cancer by means of conferences, symposia, publication of learned monographs, bibliographies, etc.

F. Provision to the National Advisory Cancer Council of special information on research grant applicants, their research problems, methods, facilities, and related research by others to the end of facilitating competent and adequate review of applications; accomplishment of this through correspondence, visits by staff, Council members and others, including members or representatives of Study Sections.

G. Presentation to the National Advisory Cancer Council of the technical evaluations and recommendations regarding research proposals for grants as made by appropriate Study Sections, or by special reviewers of research grant applications in those instances in which there is no existing Study Section competent to render this advice.

H. Maintenance of liaison and cooperation with the Division of Research Grants, National Institutes of Health, in the activities of the Study Sections in review of applications and with the Division of Research Grants and other Institutes of the National Institutes of Health in the development of policies and procedures for the administration of the total research grants program of the National Institutes of Health.

I. Maintenance of liaison and exchange of information with other governmental and non-governmental agencies in this country and abroad with like interests, responsibilities, and programs in order to promote collaborative efforts and to avoid unnecessary and undesirable duplication of effort. Organizations of this type include the National Science Foundation, American Cancer Society, Atomic Energy Commission, Office of Naval Research, Department of Defense, Department of Agriculture, Smithsonian Institution, Damon Runyon Memorial Fund, Jane Coffin Childs Memorial Fund, Anna Fuller Fund, British Empire Cancer Campaign, National Academy of Sciences and National Research Council, Rockefeller Foundation, International Union Against Cancer, American Medical Association, and numerous others.

J. Preparation of special and regular reports for the information of the National Advisory Cancer Council, the Director of the National Cancer Institute, the Director of the National Institutes of Health, the Surgeon General, the Bureau of the Budget, members of Congress and congressional committees as to special and general problems and progress in the field of cancer research, with special reference to new developments and new opportunities, or to individual applicants and actions taken on their applications.

NCI-025
PROJECT REPORT

Summary of Actions: During the calendar year 1954, research grant applications were presented to the National Advisory Cancer Council at its three meetings in February, June, and October for review and recommendation as follows:

	Number	Amount
Applications reviewed	911	$12,862,907 1/
Grants recommended 2/	744	9,953,800 1/
Applications not recommended	101	1,388,531 1/
Applications deferred, withdrawn, etc.	36	
Grants recommended but not awarded for lack of sufficient funds	29	245,692

1/ These figures do not balance primarily because some grants are recommended in amounts less than those requested by the applicants.

2/ Without distinction as to fiscal year appropriation from which they might be paid.

PROJECT REPORT FORM (Cont'd)

NCI-025
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$74,432	5	7	12	4-1/3	7	11-1/3	
FY 1956	$73,615	5	7	12	4-1/3	7	11-1/3	

BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☒ TECHNICAL ASSISTANCE ☐

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: The Division of Research Grants, National Institutes of Health, provides the part-time services of personnel and of facilities for receipt of cancer research grant applications, their assignment, duplication and preliminary technical and scientific review by Study Sections, the processing for payment of approved grants upon authorization from the National Cancer Institute, and the fiscal audit thereof. Such activities are carried on in collaboration with the staff of the National Cancer Institute.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This project parallels the research grant programs of the other categorical institutes of the National Institutes of Health and the non-categorical research grant program of the Division of Research Grants.

PROJECT REPORT FORM (Cont'd)

15. NCI-025
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Dr. C. D. Larsen was appointed as the United States representative on the Committee on International Congresses of the International Union Against Cancer.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Research Grants & Fellowships Branch
LABORATORY OR BRANCH

3. SECTION OR SERVICE

4. LOCATION (IF OTHER THAN BETHESDA)

5. NCI-026
SERIAL NO.

6. Administration of cancer research fellowships program.
PROJECT TITLE

7. R. G. Meader
PRINCIPAL INVESTIGATOR(S)

8. Cancer Research Fellowships Specialty Board.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To encourage, promote, and support the research training of well-qualified candidates in basic science and clinical fields pertinent to cancer to the end that more and better qualified investigators will be enlisted in the attack on the problems of cancer at all levels.

Methods: A. Provision of funds for the award of predoctoral, post-doctoral and special fellowships for training in research in fields pertinent to the problem of neoplastic growth.

B. Review by Central Qualification Board and Cancer Research Specialty Board of all applications submitted by candidates for fellowships in fields related to research on neoplastic growth.

C. Survey of the numbers, types, fields of study, subsequent activities and scientific progress of the candidates selected for support and of those not so selected.

D. Interviews with candidates and potential candidates.

E. Maintenance of liaison with the Office of Fellowships, Division of Research Grants, National Institutes of Health, through which the detailed administration of this program is effected and participation in the work of the Fellowships Boards in selecting candidates for the award of Fellowships.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-026
SERIAL NO.

PROJECT DESCRIPTION (Continued)

F. Maintenance of liaison and exchange of information with other governmental and non-governmental agencies in this country and abroad with like interests, responsibilities, and programs in order to promote collaborative efforts and to avoid unnecessary and undesirable duplication of effort. Organizations of this type include the National Science Foundation, American Cancer Society, Damon Runyon Memorial Fund, Jane Coffin Childs Memorial Fund, Anna Fuller Fund, National Academy of Sciences and National Research Council, Rockefeller Foundation, Commonwealth Fund, the John and Mary R. Markle Foundation, and numerous others.

G. Preparation of special and regular reports for the information of the National Advisory Cancer Council, the Director of the National Cancer Institute, the Director of the National Institutes of Health, the Surgeon General, the Bureau of the Budget, members of Congress and congressional committees as to needs, activities, opportunities, etc. for training new recruits in the scientific areas germane to cancer research.

Summary of Actions:

During the calendar year 1954 there were awarded fellowships totaling $945,840 to 242 promising young scientists who are being aided by these funds to secure advanced research training in fields bearing on the cancer problem, including many aspects of biology, chemistry, physics, and medicine. These include predoctoral fellows undergoing training in research methods and conducting research that will lead to the granting of an advanced degree (Ph.D. or its equivalent) and a career in independent investigation. The remaining are postdoctoral and special fellows who are expanding their research training and experience under the supervision of or in association with a mature scientist preparatory to taking their places as investigators and teachers in the research and educational centers of the United States. It is the constant replenishment of the pool of research manpower which enables this nation to make continued progress in medical and scientific research. Nearly 90 percent of the scientists previously trained under this program are still actively engaged in research or teaching of medical subjects related to cancer. In addition to the promise of future contributions which the fellows in training offer, they are producing significant contributions while they are still in training.

10. NCI-026
Serial No.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$ 3,243	1	0	1	1/3	0	1/3	
FY 1956	$ 3,218	1	0	1	1/3	0	1/3	

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12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☒ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

The Office of Fellowships, Division of Research Grants, National Institutes of Health, provides the part-time services of personnel and of facilities for receipt of cancer research fellowship applications, their assignment, duplication, and preliminary review as to completeness, and for interviews when feasible. The Central Qualifications Board, comprised of representatives from other Institutes as well as the Chief of this Branch, reviews applications as to their satisfaction of minimum qualification requirements, aids in assignment of applications to the appropriate Specialty Fellowship Boards for review, and sets the range for stipends for special fellowships as guides to the Specialty Boards, thus assuring some degree of uniformity of action of the Specialty Boards. Staff scientist members of research Laboratories and of this Branch of the National Cancer Institute serve as members of the Cancer Research Specialty Board for review and recommendation as to award of Cancer Research Fellowships. The Division of Research Grants completes the award for the Surgeon General and processes approved awards for payment from fellowship funds of the National Cancer Institute, and the fiscal audit thereof.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This project parallels the research fellowships grant programs of the other categorical institutes of the National Institutes of Health and of the non-categorical program of the Division of Research Grants but differs in the fields in which fellowships are awarded. Staff scientist members of research Laboratories and of this Branch of the National Cancer Institute serve as members of the Cancer Research Specialty Board for review and recommendation as to award of Cancer Research Fellowships. The Division of Research Grants completes the award for the Surgeon General and processes approved awards for payment from fellowship funds of the NCI, and the fiscal audit thereof.

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NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

Research Grants & Fellowships Branch
LABORATORY OR BRANCH

3.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-027
SERIAL NO.

6. Administration of grants for construction cancer research and training facilities.
PROJECT TITLE

7. R. G. Meader
PRINCIPAL INVESTIGATOR(S)

8. W. W. Payne
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To increase the potential for cancer research and training in research by provision of increased and more adequate space and equipment for conduct of these activities.

Methods: A. Grants of funds provided by allocation or contract authority in the Appropriation Acts of 1948, 1949, and 1950 were awarded by the Surgeon General on recommendation of the National Advisory Cancer Council. These grants were to non-Federal institutions such as universities, medical schools, hospitals, and research institutions to construct or aid in the construction of facilities for research and for training in research.

B. Technical and general information and advice was provided by the staff to the National Advisory Cancer Council to aid in review of applications, and to the grantee institutions to aid in the planning of facilities and in the securing of materials in short supply. No grants of this type have been made since fiscal year 1950 but funds provided by the Appropriation Acts of 1950, 1951, 1952 and 1953 for liquidation of contract authorization have been administered and services rendered to grantee institutions.

C. Reports on completion of facilities and on requests for other similar grants have been prepared for the information of the National Advisory Cancer Council, Director of the National Cancer Institute, Director of the National Institutes of Health, the Surgeon General, the Bureau of the Budget, members of Congress,

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT DESCRIPTION (Continued)

C. and congressional committees, as well as for citizen groups and other non-governmental agencies and foundations.

Summary of actions:

Of the total of $16,303,000 awarded for 55 projects there remained for payment during the calendar year 1954 a total of $830,401 for four grants, Payment of these balances reduced the unpaid appropriated funds to zero. These projects will be completed in the near future. The facilities provided through the other 51 construction projects have been completed and are being actively used for expanded cancer research programs supported by public and private agencies and by individual donors. It is estimated that the facilities constructed with the aid of the $16,303,000 appropriated by Congress for this purpose required the expenditure of an additional $118,785,035 obtained by the grantees from other sources for their completion, exclusive of the value of the land or of other facilities already owned or used by the grantee institutions. It is evident that these governmental funds did not discourage the provision of similar contributions from non-Federal sources but, on the contrary, were a stimulus to securing many times their total from such non-Federal sources. Furthermore, a survey of cancer research grants from the major agencies supporting cancer research indicates that institutions receiving such construction grants have requested and received a much greater proportion of the total research grant funds over the past four years than did those institutions which did not request or did not receive construction grants. Since there was no conscious or intentional action by the agencies to make this discrimination in research grant awards, it is assumed that these correlations reflect the interest of certain institutions to expand their cancer research efforts by addition of qualified personnel, by increased activity of personnel already employed, and by expansion of facilities in which their investigators could work. The correlations may also reflect an attraction for the more highly qualified scientist to institutions where conditions for his research are most favorable. At the end of 1954 the National Cancer Institute had on hand formal or informal requests from 83 institutions for construction funds in the amount of approximately $30,000,000.

PROJECT REPORT FORM (Cont'd)

10. NCI-027
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$1,537	0	1	1	0	1/3	1/3	
FY 1956	$1,512	0	1	1	0	1/3	1/3	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☒ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Personnel for the technical administration of the construction grant program during its wind-up phase in 1954 and 1955 has been provided on a limited part-time basis by the office of the Associate Director of the National Cancer Institute in charge of Research.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

The project herein described was paralleled by a similar project supported by the appropriation for the National Heart Institute which was given technical administration by the same personnel. This provided for a collaboration and integration of activities of the two projects which, in some instances, supported the construction of common facilities for the two research programs. Through this joint technical supervision and collaborative grants for construction of joint facilities many economies have been effected. The fiscal management of the funds for this project has been accomplished jointly with the Division of Research Grants, National Institutes of Health.

NO ENTRIES IN 15, 16 & 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Office of the Chief
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-100
SERIAL NO

6. Clinical Traineeships program
PROJECT TITLE

7. R. F. Kaiser, Medical Director
PRINCIPAL INVESTIGATOR (S)

8. Mary W. Brunot
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this program is to provide support for graduate physicians in training centers throughout the country which will permit them to secure special training in the diagnosis and treatment of cancer. Under this program physicians who have made satisfactory arrangements with training centers for securing such special training apply to the branch for traineeship support. Such applications are reviewed by a traineeship board consisting of 5 individuals (4 professional and 1 nonprofessional) and those candidates who are selected for support are appointed and paid directly by the NCI. Successful candidates receive $3,600 annually.

During the year 160 trainees were supported in 71 institutions. Through the provision of this training it has been possible to increase the quantity and quality of cancer services and facilities available in the country and to improve the management of cancer cases by the physician.

Continuation of the program at its current level is anticipated.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-100
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,611	0	1	1	0	1	1	0
FY 1956	$4,539	0	1	1	0	1	1	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☒ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-100
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The Clinical Traineeship Program of the National Cancer Institute
Raymond F. Kaiser, M.D. Public Health Reports, Vol. 69, No. 8,
pp 776-780, August 1954.

---------------- PARTIAL LIST OF
PUBLICATIONS PREPARED AND PRESENTED BY N.C.I. TRAINEES:

Minn. Med. Vol. 37: pp 243-250, Apr. 1954. Cancer Detection. Claude R. Hitchcock, M.D., & J. Bradley Aust, M.D., NCI Trainee

J. of Oral Med. Surg. & Path. Palatine Minor Salivary Gland Adenocarcinoma. R. W. Christensen & R. A. Blossom, NCI Trainee

Paper on Vaginal Discharge. N.Y. Academy of Med. fortnight on infections. Diag. of Med. C. M. Donnenfeld.

Toxicity of Versene (Sodium ethylene diamine tetracitrate) decontamination drug for objects of ind. exposed to radioactive heavy metals, etc. Report of autopsy findings & rev. of lit. of 2 cases of adult agamma globulinenia. H. Robert Dudley.

Biological Studies on Stable and Radioactive Rare earth compounds. Distribution of Radioactive Yttrium in normal and ascites tumor bearing mice and in cancer patients with serous effusions. J.N.C.I. Joseph Greenberg.

Lynogisarcina of the lung (report of 3 cases & rev. of the Amer. Lit.) Simple benign epithelial cysts of the skin (clarify pathogenesis & nomenclature of such cysts.) Robert E. Klein.

Rev. of all cases of pancreatic carcinoma at Temple U. Hosp. Geo. F. Mock.

Thyroid Carcinoma. Earl R. Miller & Harry S. Oden. U. of C. Med. Center.

Polypoid neoplasms of the stomach. Leonard Asher & James A. Sargent. Use of Radiation & Radiomimetric agents in CA Therapy. N.B. Friedman & James A.Sargent.

Rev. of Lit. on the Etiology of CA of Cervix. Wm. L. Williams.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

2. Grants Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-101
SERIAL NO.

6. Training Grants
PROJECT TITLE

7. N. B. Hon
PRINCIPAL INVESTIGATOR(S)

8. Raymond F. Kaiser, William S. Baum
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To improve the teaching of cancer in undergraduate school of medicine, dentistry and osteopathy.

Methods employed: The training grant program makes available funds in amounts up to $25,000 for approved 4 year medical and osteopathic schools and not to exceed $5,000 for approved 4 year dental schools and 2 year medical schools for the integration of teaching of cancer throughout the curriculum of the schools.

Major findings: This program has been in operation 7 years. During the calendar year 1954, 82 medical, 42 dental and 6 osteopathic schools participated in the program. A total of $2,274,754 were made available for this program.

This program has been responsible for the establishment of a coordinator of cancer teaching in all of the medical, dental and osteopathic schools, and cancer committees have been formed in a majority of them.

The evaluation of this program is accomplished through the provision of a cancer learning test program in which a large number of schools compete. The results of the test indicate that there has been a significant increase in the students knowledge of cancer as compared with the beginning or early years of the program.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-101
SERIAL NO.

Significance to the program: The results of this program has been to increase the overall awareness of the cancer problem in the young physician. With this increased awareness, physicians better trained cancer diagnoses and treatment will be reflected in better management of the cancer patient.

Proposed course of project: It is proposed to continue the program at the present level and to include all of the new schools and those being organized and established, without modification of the amount of funds currently available for each type.

PROJECT REPORT FORM (Cont'd)

10. NCI-101
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$9,391	1	2	3	1/3	1 1/3	1 2/3	
FY 1956	$9,270	1	2	3	1/3	1 1/3	1 2/3	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☒ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-101
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Results of the Cancer Teaching Program in Medical Schools, December 1954, Public Health Reports, Vol. 69, No. 12.

Some Results of the Cancer Teaching Program in Dental Schools In Press - Public Health Reports, January 1955.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Grants Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-102
SERIAL NO.

6. Field Investigation Grants
PROJECT TITLE

7. N. B. Hon
PRINCIPAL INVESTIGATOR (S)

8. Raymond F. Kaiser, William S. Baum
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This activity provides support for field investigation projects, applied and developmental research, community studies and surveys, and pilot projects, all of which contribute to methods for the prevention, control, diagnosis and treatment of cancer. Although each grant awarded has a specific objective, the overall goal of this program is to decrease the time involved between the discovery of new cancer knowledge in laboratories, clinics and hospitals, and the application of this new knowledge throughout the country to the prevention, diagnosis and treatment of cancer in patients.

Methods employed: Applications for the support of studies are received and processed, then reviewed by the Cancer Control Committee and recommended for approval by the National Advisory Cancer Council. Through this mechanism arrangements have been developed with a large number of organizations and institutions throughout the country.

Major findings: Funds available for distribution during the calendar year 1954 were $1,100,000.

A total of (110) applications were received during the year. 78 of these were approved by National Advisory Cancer Council, totaling an expenditure of $1,194,685. Of this approved number, 16 were new grants, totaling $327,733; 59 were continuation projects amounting to $858,524 and 3 supplemental grants totaling $8,428.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

The projects supported were distributed chiefly among five major areas of investigation (1) environmental cancer studies (2) development and evaluation of cancer diagnostic tests (3) etiology of lung cancer (4) medical and nursing education (5) cancer therapy.

A number of outstanding accomplishments have resulted during the year.

It has been demonstrated that the vaginal aspiration is an efficient diagnostic aid in detecting uterine cancer. Preliminary data indicate that this method is particularly effective in the early or in-situ cancer cases, thus enabling these cases to be detected before physical signs or symptoms become apparent. The data, in addition, suggest that carcinoma-in-situ occurs at an early age (peak at 30-34), and remains localized for a period in excess of ten years. This indicates that the widespread application of this method in case finding, in the great majority of cervical carcinoma, will result in curative therapeutic procedures before the stage of invasion occurs. Thus, it now appears possible to greatly reduce, and to a great extent eliminate cancer of this site as a major contributing cause of mortality in the female.

A major contribution has been that made by (Meigs) in his studies utilizing a combined approach by industry, field investigations, and animal research. His contributions have included the observation that the portal of entry of benzidine and other amines is directly through the intact skin; the source may be previously contaminated apparel (boots). The concept that metabolites of benzidine may be an important factor in the causation of bladder cancer indicates the importance of this work.

The first step in the instrumentation phase of the remote Flouroscopic control of Roentgen therapy was completed (Morgan). This was a new remotely operated screen intensifier of a type which yields results considerably better than previous instruments and is now being adopted to a 250 Kv constant potential therapy machine.

Examination of a hospital population by the modified tubeless gastric analysis, (Segal) and correlation of the findings with the urine uropepsin content and gastro-intestinal X-ray studies, offer hope for a simple screening procedure to detect gastric achlorhydria. This gives promise of potential aid in combating the difficult problem posed by gastric cancer.

The educational films, produced under the joint sponsorship of the National Cancer Institute, and the American Cancer Society, Inc., have continued. The "Warning Shadow", and educational film on lung cancer for lay personnel has been completed, to join the film on Breast Self Examination in this group. Completed films for the education of professional audiences include "Cancer: The Problem of Early Diagnosis", and similar type films on the specific sites of Breast, Uterus and the Gastro-Intestinal Tract.

NCI-102
SERIAL NO.

Contributions of promise have resulted from careful and detailed pathologic studies on carcinoma of major sites (breast, lung, stomach, prostate, uterus, etc.) by McGrath. Results indicate that a high proportion of malignant tumors are multicentric in origin (lung 28%, stomach 33%) and in addition a high proportion show varied histologic patterns. The significance of these findings to therapeutic surgical procedures, and the problem of recurrence may be of the greatest importance.

Publications include the following:

1) Bronchogenic Carcinoma. A product of Multiple Sites of Origin - McGrath, Gall, Kessler - Journal of Thuracic Surgery 24: 3: 271: September 1952.

2) Histologic Grading of Colon Carcinoma
Valid Procedure - Qualheim and Gall.
A,M.A. Archives of Pathology 56: 466: Nov. 1953.

3) Pre Invasive Carcinoma and Pre Cancerous Metaplasia of the Cervix - Carson and Gall
American Journal of Pathology 1954 XXX: 1: 15.

Geographic studies of utering carcinoma (Grinberg) indicate that the incidence rate for cancer of the corpus in the Jewish population of Israel is the same as it is in the non-Jewish white population of the United States, but the incidence of cancer of the cervix is definitely less. Accurate data such as these offer much hope in developing needed information on the etiologies and pathogenesis of carcinoma in humans.

Detailed metabolic studies on patients with advanced cancer (Elman) have provided data on nitrogen balance and the influence of steroid and hormone therapy which may be of great practical importance in the nutritional care and rehabilitation of any malnourished patient, with or without cancer. Publication on a portion of this study may be noted in:

Publications: Surgery 34: 874: 1953 (November)
Utilization of Exogenous Protein in Cancer and Non-Cancer Patients.

Many additional studies of great potential value to the patient are now being carried on. The findings from these will be tabulated in future reports.

Significance to the Cancer Institute: It is estimated that complete application of knowledge now available to the point of maximum efficiency would reduce the present cancer mortality rate by an additional 25 percent. Grants awarded under this program are to develop procedures to a point where they can be applied; to test the applicability of methods on a community basis; to demonstrate the desirability and

thereby encourage the adoption of the newest methods; and to make the latest information available to physicians and the lay public.

Proposed course of project: Special emphasis will be continued in the search for diagnostic tests and methods of discovering the disease at an earlier stage in the general population. Progress that is made in the development of therapeutic measures will be evaluated and demonstrated on a mass trial basis as early as possible. Example of a few of the grants awarded under this program are the Memphis-Shelby County cooperative screening project to demonstrate the value of the Papanicolaou technique in discovering cancer in a stage at which it is practically 100 percent curable; grants made to laboratories in Pennsylvania, California, Illinois, Utah and Connecticut in search of environmental factors that may be important in the development of cancer, and special studies supported in Arkansas, Georgia, Washington, California and other States to further develop the special techniques of cytologic diagnosis and to continue observations of the occurrence of cervical cancer in the general population.

PROJECT REPORT FORM (Cont'd)

10. NCI-102
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED	BUDGETED POSITIONS			MAN YEARS			PATIENT
	EXPENDITURES	PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
FY 1955	$20,486	1	3	4	1	2 1/3	3 1/3	
FY 1956	$20,246	1	3	4	1	2 1/3	3 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☒ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Grants Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5.NCI-103
SERIAL NO

6. State Aid Grant
PROJECT TITLE

7. N. B. Hon
PRINCIPAL INVESTIGATOR (S)

8. Raymond F. Kaiser, William S. Baum
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To provide financial support for the establishment of cancer diagnostic and treatment facilities, development of more adequate reporting and follow-up systems for cancer patients, increase cytologic and tissue diagnostic laboratory services, extend lay and professional educational activities.

Methods employed: Grant funds are distributed on a formula basis which takes into consideration four factors: population, financial need, population density and the extent of the cancer problem based on cancer mortality. These funds become available on the submission of an approved program plan and on matching of grant funds by the State, one dollar for each two dollars of grant funds.

Major findings: Each of the States and Territorial Health Departments have submitted semi-annual activity reports on their programs during this calendar year. A summary of these reports indicated that 40 of the States and Territories engaged in a diagnostic and treatment clinic program; 28 States provide cytologic and tissue diagnostic laboratory services; 36 States conduct lay and professional education activities. All of the States and Territories (53) furnish cancer nursing services to some extent.

A total of 388 diagnostic and treatment clinics are supported through this program. This number of clinics examined 24,510 persons for cancer for the first time. 12,845 patients were found to have cancer. Of this number 61% were found to have cancer in a localized

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

stage; 27% had regional metastasis; 12% had remote metastasis. There were 32,469 tissue diagnostic examinations made, 21% of which were positive for cancer. 31,830 cytological laboratory examinations were performed, 4% of which were positive.

The outstanding problem of this program is the lack of professional personnel, particularly medical, to develop and administer the programs within the States.

Significance to Cancer Program: In order to obtain the prevention, control and eradication of cancer, it is necessary to provide adequate cancer facilities and services within the States. This program offers a means for the provision of these needed services and permits the extension of pertinent findings in cancer investigation and research to the people.

Proposed course of project: During the next calendar year emphasis in the program will be directed toward (1) the employment of qualified medical personnel, wide spread use of cytology as a case finding procedure for cervical cancer, the establishment of clinic registers as a means of improving follow-up of cancer patients and of obtaining better reporting and cancer survival information.

PROJECT REPORT FORM (Cont'd)

0. NCI-103
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$47,616	2	8	10	2	7 1/3	9 1/3	
FY 1956	$53,935	2	8	10	2	7 1/3	9 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

NONE

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE

PROJECT REPORT FORM (Cont'd)

15. NCI-103
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 195

Comments on Cancer Control Program
In Press - Journal of the Medical and Chirurgical Faculty

Significant Developments in Cancer Research -
To be published in the quarterly bulletin of Wisconsin State Board of Health entitled "Health"

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

1. N.C.I.
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Office of the Chief

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-104
SERIAL NC

6. Radium Loan Program
PROJECT TITLE

7. R. F. Kaiser, Medical Director
PRINCIPAL INVESTIGATOR (S)

8. Mary W. Brunot
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this program is to make available to qualified radiologists in approved hospitals radium on an annual contract loan basis. Practically all available radium--approximately 9 grams--in various types of applicators has been on loan to 54 institutions in 30 states, including the District of Columbia.

This program makes it possible for patients whose financial circumstances would otherwise prevent it, to receive radium therapy.

Program is to be continued without change.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-104
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,293	1	1	2	1/3	1/3	2/3	0
FY 1956	$4,745	1	1	2	1/3	1/3	2/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

National Bureau of Standards

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Nursing Section
SECTION OR SERVICE

4. T-6
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-105
SERIAL NO.

6. A Cancer Nursing Study in Forty-Nine Public Health Agencies
PROJECT TITLE

7. M. Dolores Howley
PRINCIPAL INVESTIGATOR (S)

8. Sidney J. Cutler and Benjamin E. Carroll, Statistician, Biometry Section
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective:

(1) To obtain and analyze data from nursing agencies in various geographic areas which might be used to determine the nursing problems involved in care of cancer patients in the home and the administrative problems in operating a cancer nursing service.

(2) To develop materials which may be of value in program planning.

Method:

(1) Public Health agencies rendering bedside nursing service (to cancer patients) were invited through the regional offices of the Public Health Service to participate in the study.

(2) Agencies were supplied with cards for recording data. Directions accompanied the card to promote uniformity and accuracy in the collection of data.

(3) The collection of data extended from November 1, 1951 through April 30, 1952.

(4) Two thousand four hundred and thirteen cards were received for processing.

(5) In several instances, for basic comparison, data were used from a series of cancer morbidity studies covering ten major cities in the United States.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-105
SERIAL NO.

Major Findings

(1) The results of 49 agencies which included 3 official agencies - 11 semi-official, and 35 non-official agencies of various sizes compared favorably with the studies of large non official agencies in our large cities like New York and Philadelphia.

(2) That only a small percent of the total case load is cancer .

(3) That cancer and chronic disease patients require a longer visit than the average patient.

(4) That the average length of time requiring nursing service is three months.

(5) That approximately one-fourth of the patients dies within one month after the public health nurse's first visit.

(6) That the median visits per week for all patients was 2.0

(7) That patients with cancer require only general nursing care requiring relatively few visits.

Significance to F. I. D. B. Nursing Section:

(1) As the incidence of cancer is increasing it is anticipated that more cancer patients will receive care in the home.

(2) This study will enable F.I.D.B.

  a. To give assistance to Nursing Directors in estimating the anticipated cancer caseload

  b. To emphasize that the integration of cancer nursing in the generalized programs will not demand an excessive amount of nursing service or highly specialized skills

Proposed Course of Project

(1) Detailed reports of the study have been sent to each agency participating in the study

(2) A condensed report of the study will be printed in either Public Health Reports or in one of our national nursing journals

10. NCI-105
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED ESPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,389	1	0	1	1/2	0	1/2	0
FY 1956	-------	0	0	0	0	0	0	0

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12. BUDGET ACTIVITY:

RESEARCH ☐ Administration ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 195

49 agencies and the Regional Offices of the Public Health Service and the Directors of Public Health Nursing from most of the State Departments of Heal

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstration Branch
LABORATORY OR BRANCH

3. Nursing Section
SECTION OR SERVICE

4. ____________________
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-106
SERIAL NO.

6. Work Conferences for the Deans of Nursing, Cancer Nursing Project Directors, Chairman or faculty representatives of Curriculum Committees from the 5 University Schools of Nursing which are recipients of Cancer Special Grants.
PROJECT TITLE

7. Rosalie I. Peterson and Margaret F. Knapp
PRINCIPAL INVESTIGATOR(S)

8. Dr. Louis Heil, (Consultant)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To develop instruments for the evaluation of cancer nursing in the basic professional nursing curriculum.

Methods Employed:

1. Securing the services of a specialist in the field of evaluation and educational research to serve as a resource person for the work conference.
2. Through general discussion defining specific areas needing development.
    - a) Knowledge and Achievement Test
    - b) Attitudes and Understandings
    - c) Annual Report
    - d) Problem Solving
    - e) Patient and Family Reaction
3. Participants formed three sub groups - each group selecting one of the areas for concentrated work.

Major Outcome

1. A knowledge test in cancer begun by the cancer nursing project director at Skidmore College was refined. 85 new options were revised or replaced.

   The tests will be given to all of the nursing students in each of the five university schools of nursing in order to validate the options and to test the reliability of the tool. It then will be ready for general use in schools of nursing.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-106
SERIAL NO.

2. The group on Attitudes and Understandings developed their instrument by the use of records in which the role of the nurse in caring for patients were dramatized. Three episodes were selected for development reflecting detection, early treatment, and rehabilitation.

The third group developed are Annual Report Form which would reflect progress and change.

Significance to Cancer Field Investigations and Demonstrations Branch - Nursing Section

The tools developed in the work conference will aid in evaluating student nurse attitudes, nursing skills, and cancer knowledge. When refined sufficiently, these tools can be used generally in the field of nursing. It is felt that knowledge in cancer will increase among nursing faculty members, nursing service personnel and students where the tests are administered. This should reflect in earlier case finding, larger survival groups and greater rehabilitation of patients.

Proposed Course of Project

Refinement of present tools. Further work conferences to develop tools of evaluation in other areas such as Problem-Solving and Patient/Family Reactions.

PROJECT REPORT FORM (Cont'd)

10. NCI-106
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$8,779	2	0	2	1	0	1	0
FY 1956	$9,455	2	0	2	1	0	1	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Five University Schools of Nursing Receiving Special Project Grants from F.I.D.B. - Skidmore College, New York; Boston University; Washington University, St. Louis, Mo.; Vanderbilt University, Nashville, Tenn.; and U.C.L.A.

Dr. Louis Heil, Director of Dept. of Evaluation and Educational Research, Brooklyn College, New York (Consultant to Nursing Section, F.I.D.B.)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstration Branch
LABORATORY OR BRANCH

3. Nursing
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-107
SERIAL NO.

6. Consultation Service to five Universities receiving special project grants from NCI
PROJECT TITLE

7. Rosalie I. Peterson and Margaret F. Knapp
PRINCIPAL INVESTIGATOR(S)

8. Dr. Hon
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective:

A. To give assistance to the Cancer Nursing Project Directors at Skidmore College, New York; Boston University; Washington University, St. Louis; Vanderbilt University and UCLA in accomplishing the (1) Integration of Cancer Nursing in the Basic Professional Nursing Curriculum
   (2) Teaching a broad concept of cancer which would include knowledge of cancer and its problems, prevention, early detection, treatment, nursing care in hospital and home, and rehabilitation
   (3) Using the monograph, "Cancer Nursing in the Basic Professional Curriculum" as a guide
   (4) Exploring the use of the problem solving as a method of teaching

B. Assist in refining and improving the Knowledge Test to evaluate the learning of cancer by student nurses

Method:

A. Visits to the grantee schools and meeting with the total nursing faculty to:
   a. discuss problems encountered in the study
   b. share in the interpretations and aid in solving some of the problems
   c. learn from them methods of overcoming obstacles
   d. observe nurse-patient relationships in the hospitals and clinics

B. Conduct work conferences so that all of the project directors
   a. may attach mutual problem
   b. may develop tools of evaluation

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-107
SERIAL NO.

Major Finding

1. Cancer is a desirable disease area in which to teach the basic principles of nursing
2. Cancer is an excellent area in which nurses may learn to give skilled comprehensive nursing care to a patient and his family
3. It is extremely difficult to change a curriculum pattern which involves a total faculty and may involve philosophy
4. There must be wholehearted faculty participation of total integration of a disease entity is to be accomplished.

Significance to F.I.D.B. - Nursing Section

If cancer can be integrated throughout the basic professional curriculum, nurses will have greater knowledge of cancer, which should reflect in earlier case finding and better support of the patient and his family.

Proposed course of project

Continue evaluation and support of the project through the remaining 2 1/2 years of the five year pilot study.

Depending upon the results of the pilot study, determine whether further expansion of this method of teaching should be planned for and encouraged or whether a new approach is needed.

PROJECT REPORT FORM (Cont'd)

10. NCI-107
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$8,779	3	0	3	1	0	1	0
FY 1956	$9,455	3	0	3	1	0	1	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Five University Schools of Nursing Receiving Special Project Grants from F.I.D.B. - Skidmore College, New York; Boston University; Washington University, St. Louis, Mo.; Vanderbilt University, Nashville, Tenn.; and U.C.L.A.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Nursing
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-108
SERIAL NO.

6. Cancer Nursing Institutes
PROJECT TITLE

7. Rosalie I. Peterson; Dolores Howley
PRINCIPAL INVESTIGATOR(S)

8. F. Ruth Kahl
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective

(1) To improve and extend knowledge regarding cancer among nurses.
(2) To stimulate further study in cancer
(3) To help nurses become more alert to detect symptoms and signs of cancer among constituents served by them.

Methods Employed

Responsibility for planning of institutes vested with local committee. Preplanning visit made when possible and if not possible, assistance given through correspondence and by telephone.

Institutes were of one or two days duration.

Attendance ranged from fifty to three hundred and fifty.

Lectures, visual aid, role playing and group projects were methods used at most sessions.

One series combined heart, tuberculosis, and cancer nursing.

Institutes were conducted in Iowa, Tennessee, Georgia, Arizona, Oregon, Washington, Missouri, Kansas, and New York City.

(continued p.2)

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-108
SERIAL NO.

Major Findings

Difficult to evaluate results. There is evidence of tremendous enthusiasm at the time of the meetings and by the planning committee in the post evaluation conference.

Significance to Cancer Nursing Section

Institutes bring together nurses from universities, hospitals, industry, and public health. We find nurses who are able to serve as resource people for other educational activities in local communities. Occasionally we find universities and schools of nursing which are willing and able to test the reliability of the educational tools we are developing.

Proposed Course of Project

To encourage planning group to conduct their own cancer nursing institutes if resource persons are available

PROJECT REPORT FORM (Cont'd)

10. NCI-108
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,389	2	0	2	1/2	0	1/2	
FY 1956	$4,727	2	0	2	1/2	0	1/2	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Regional offices - public health nursing consultants, State departments of Health, directors and consultants of public health nursing.

State Divisions of the American Nurses Association and of the National League for Nursing.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Many States sponser institutes

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Nursing Section
SECTION OR SERVICE

4. T-6
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-109
SERIAL NO.

6. Demonstration of the Development of an Effective Cancer Nursing Consultation Servic
PROJECT TITLE through integration of cancer in each of the existing specialized
consultant's programs.)Iowa
)Oklahoma

7. F. Ruth Kahl, Senior Nurse Officer
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Objectives - extension and improvement of public health nursing service to cancer patients through an effective cancer nursing consultation service. The public health nursing service includes 1) finding patients with signs or symptoms suspicious of cancer and following such patients until medical care is secured; 2) nursing care to patients on a demonstration basis with continuing care as needed; 3) counseling to enable patient and family to solve their problems until patient has reached maximum rehabilitation; 4) educational activities.

Methods -
a) Study of present cancer nursing activities by local public health nurses, by supervising nurses and by nursing consultants via review of reports and selected observations in local areas
b) review of activities of each specialized consultant nurse with consideration of cancer nursing consultation which might be extended.
c) group action to determine activities of each consultant, methods, and time for demonstrations

Major Findings:
a) Nine operating cancer clinics in the State - have never been visited by any of the nurses
b) Reports of each patient diagnosed in these clinics are sent to the Department of Health but to date these reports have not been utilized for follow up
c) Major nursing service has been in relation to terminal care of cancer patients - attitude both of patients and of local nurses is inclined to be that of pessimism regarding prognosis of any patient with cancer

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

of any patient with cancer

Facts a) b) and c) were pertinent factors in determining activities of the consultants.

Significance of this project to the program of the Institute.

a) We believe that public health nurses may contribute to earlier case finding. Consequently, a new report form has been designed and once each month the nurses will report 1) Patients, 2) date and 3) reason for referral to physician 4) date seen by physician and 5) diagnosis. Inservice education programs will be developed to meet the particular needs of the nurses in the various areas of the State.

b) Prompt follow up until diagnosis is established for patients referred by the tuberculosis surveys because of suspicious lung lesions. Follow-up of patients referred by the cancer clinics, with the consent of the physician in charge, to learn about and to assist in solving the problems of the cancer patient and his family. This may involve more home nursing of the cancer patient by the public health nurse or through arrangements with which she will assist the family.

c) Increased assistance with such rehabilitation as may be possible for each cancer patient referred to the nurse, particularly those patients referred by the cancer clinics but not formerly referred to the nurse.

d) Intensified educational activities for the citizens of the State should result in shortening the period of patient delay in seeking medical care.

Proposed Course of Project

One year probably beginning with January 1955.

PROJECT REPORT FORM (Cont'd)

10. ~~Not applicable~~ NCI-109
SERIAL NO.

~~not applicable~~

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 5,851	1	0	1	2/3	0	2/3	0
FY 1956	$ 6,303	1	0	1	2/3	0	2/3	0

~~not applicable~~

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

~~not applicable~~

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

No previous project of this type

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Nursing Section
SECTION OR SERVICE

4. T-6
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-110
SERIAL NO

6. Cancer Nursing Bibliography
PROJECT TITLE

7. Margaret F. Knapp
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Annotated bibliography on articles, books, bulletins, films and other visual aids.

(1) Objectives: The objective of this project is to compile an annotated bibliography on printed materials and visual aids for nursing educators in basic and advanced nursing programs.

(2) Methods Employed: The bibliography is a compilation of information entered on individual filing cards.

(3) Significance to Cancer Nursing: Provides references which will enable nursing instructors to improve their cancer nursing instruction.

(4) Proposed course of project: The bibliography is distributed to the 1200 nursing schools in the country and to all universities offering advanced nursing programs, and to individual nursing educators and administrators upon request.

This is a continuous project and will be revised and expanded biennially.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-110
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 7,919	1	0	1	1/3	0	1/3	0
FY 1956	$ 3,152	1	0	1	1/3	0	1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Memphis, Tennessee
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-111
SERIAL NO

6. The Memphis-Shelby County Cytology Survey.
PROJECT TITLE

7. Richard Malmgren, M.D.
PRINCIPAL INVESTIGATOR(S)

8. W. S. Baum, M.D. and S. J. Cutler
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives.

The Memphis-Shelby County Cytology Project has as its aim the examination of at least 100,000 of the 160,000 females over the age of 20 in the Memphis-Shelby County area. The objectives of this study are:

1. To evaluate the vaginal aspiration as an efficient screening test for uterine cancer.

2. To determine the effectiveness of the widespread application of this method as a case-finding procedure for uterine cancer.

3. To obtain definitive information bearing upon:

    a) The incidence of carcinoma-in-situ.
    b) The duration of carcinoma-in-situ.
    c) The course of carcinoma-in-situ, with particular regard to its progression into an invasive malignant lesion, and to its remission if any.

(B) Methods.

A morbidity survey was conducted in the Memphis-Shelby County area in 1950 and in 1951, to obtain baseline data upon the frequency of occurrence of carcinoma-in-situ and invasive carcinoma of the uterine tract. Following the completion of this survey, in July 1952 the Memphis-Shelby County Cytology Project was begun, and patients were examined with the cooperation of private physicians, clinics, and the health department. The examination consists of the taking of a vaginal aspiration for cytological study upon each one of the patients in the survey, with follow-up examinations including

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION (Continued)

(B) Methods (Continued)
biopsy where indicated done on all suspicious and positive cases. After a lapse of one year, patients are re-examined by the same cytological technique. The project will be continued until a third screening examination has been completed. At the conclusion of this, a repeat morbidity survey will be conducted in this area, so that the results of the study may be further evaluated. During the calendar year of 1954, over 57,000 smears have been done on somewhat over 46,000 patients. Since the inception of this program, over 123,000 smears have been completed on over 103,000 patients.

(C) Major Findings.
Analysis of data collected on the first 70,000 subjects screened reveal that 1,076 biopsies have been completed. Of these, 544 were positive for malignancy, 282 representing intra-epithelial cervical carcinoma, 245 representing invasive cancer, and 17 representing other genital cancers. In addition, 129 biopsies were borderline or suspicious requiring repeat examination, 34 were inadequate and required repeat examination, and 369 were negative. Of the over-all total, 60 percent of the carcinomas found were unsuspected prior to the cytologic examination, and in the intra-epithelial or carcinoma-in-situ group, nearly 90 percent were unsuspected.

(D) Significance To Cancer Research.
This project to date indicates that the vaginal aspiration is an efficient method of detecting cancer of the uterine tract. It will, in addition, furnish more definitive data upon the frequency and the course of carcinoma-in-situ. The findings are of particular significance since preliminary findings indicate that this simple and easily applied technique gives great promise, if not of completely obliterating, at least of greatly reducing the mortality from uterine cancer, if it is applied generally on a mass basis. Since cancer of the uterine tract represents one of the major sites in women, it now appears almost certain that this project will furnish the data which is necessary to launch a widespread and integrated attack upon this disease.

(E) Proposed Course of Project.
Studies in 1955 will include further screening of new patients, as nearly as possible the completion of the second screening examination, and late in the year the initiation of the third screening examination. Preliminary data indicate that approximately 47 percent of the initially screened population will return for the second screening, and that approximately 75 percent of the groups screened twice will return for a third examination.

PROJECT REPORT FORM (Cont'd)

10. NCI-111
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$152,112	2	28	30	2	28	30	0
FY 1956	$157,501	2	29	31	2	29	31	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

The Department of Pathology and the Department of Obstetrics and Gynecology of the University of Tennessee School of Medicine, the Shelby-County Health Department, the Memphis and the Bluff County Medical Societies, and the Local Division of the American Cancer Society. In addition to this, participation of individual private physicians is now accounting for approximately 50 percent of the patient load in this study.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No other similar mass survey is being conducted within the Public Health Service.

PROJECT REPORT FORM (Cont'd)

15. NCI-111
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Dunn, J. E.; The Relationship Between Carcinoma-In-Situ and Invasive Cervical Carcinoma. Cancer 6(5): 873-886, 1953.

Dunn, J. E. and Rowan, J.; Uterine Cancer Illness in Memphis and Shelby County, Tennessee. Public Health Reports 69(3): 269-274, March 1954.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-112
SERIAL NO

6. Clinical Trials Unit.
PROJECT TITLE

7. Andrew C. Peacock, M.D.
PRINCIPAL INVESTIGATOR(S)

8. Miss Highsmith
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project. The development and evaluation of general cancer diagnostic tests exclusive of cytology, relating to biochemical and immunologic procedures.

(A) Objectives.
To develop tests capable of aiding in the detection of cancers of all sites in early stages of development. The over-all aim is to develop one or more cancer diagnostic tests, that will be simple, inexpensive, easily duplicated, and therefore applicable to large population areas on a mass basis.

(B) Methods Employed.
Basic research is employed upon chemical and immunological principles underlying tests previously described in the past, and principles which aid in the development of new tests. During the past year, the basic principles upon which some general tests for diagnosis have been based, have been evaluated. Modifications of these principles have been attempted, and new procedures have been adopted which may aid in the formulation of new test procedures. Procedures developed are evaluated upon the serum from known cancer patients, and from normal people.

(C) Major Findings.
During the past year the Fuchs cancer test has been studied. Since this test was widely quoted in the literature, it was felt that the fundamental observations by Fuchs, upon which the principles of this test are based, should be retested. These tests involve studies upon serum and fibrin, and heterologous serums. After careful study of the materials at hand, and repetition about 20 times, it was not possible for the fundamental observations to be duplicated. For this reason it was recommended that the test be not

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM

9. PROJECT DESCRIPTION

(C) Major Findings (Continued)

considered further, and it was concluded that this test was not a valid one.

A substantial body of data was collected upon the Penn Test. The results to date conclude approximately 500 determinations on approximately 118 personnel. The experience to date has been discouraging, but it is necessary to conduct a few experiments with the originators of this procedure before definite conclusions can be reached.

Further study has been done on the serum acid phosphatase, and the modifications used to detect the prostatic acid phosphatase in the serum. Approximately 200 to 300 such tests have been made, and new developments, particularly along immunological lines of antigen and antibody reaction have been tried. Data to date indicate that the modifications are of value in eliminating high values not due to prostatic cancer, and further data is needed to test the efficacy of the method in making earlier diagnoses.

(D) Significance to Cancer Research.

The development of any test that would aid in the detection of cancer in an early stage of one of more sites would be of an estimable value to the clinician. With strong suggestive evidence at hand that the patient has a cancer, the present diagnostic procedures could be intensified in studying this patient, and there would be impetus for the development of further refined diagnostic procedures. It is evident that the development of such tests would be of great practical value in combating the cancer problem.

(E) Proposed Course of Project.

It is proposed during the coming year, that further studies will be undertaken to further ascertain the status of the Penn Test. In addition, it is planned that fundamental observations will be made upon the new optical density test, and in addition, further studies on the modified prostatic phosphatase test will be continued. In addition, procedures for the development of new tests will be undertaken.

PROJECT REPORT FORM (Cont'd)

10. NCI-112
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$12,882	1	1	2	1	1	2	0
FY 1956	$ 14,234	1	1 ~~2~~	2 ~~3~~	1	1	2	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

The Department of Pathology of the Clinical Center, cooperates with the Field Investigations and Demonstrations Branch in this project.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No other similar work is being carried on within the Public Health Service.

15. NCI-112
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. A paper describing fundamental observations on the Fuchs Test is now in review for clearance for publication.
2. The Menkes "Pentolysis" Reaction. Public Health Monograph No. 12, page 5, 1953.
3. Plasminogen as a Test for Malignant Neoplastic Disease. Public Health Monograph No. 12, page 37, 1953.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigation & Demonstrations Branch
LABORATORY OR BRANCH

3. Field Study Section
SECTION OR SERVICE

4. San Francisco, California
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-113
SERIAL NO

6. Changes in blood as a method of diagnosis in cancer of human beings.
PROJECT TITLE

7. J. E. DUNN
PRINCIPAL INVESTIGATOR(S)

8. S. Greenhouse
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objective

1) To evaluate the specificity and sensitivity of a serum flocculation test (Penn Test) for use in mass population screening to detect presence of cancer of any site in individuals.

b. Methods Employed

1) A selected group of approximately a dozen hospitals and laboratories across the country are participating in this field trial of the Penn Test.

2) A questionnaire suitable for biometric coding for use of the laboratories was prepared, tested, evaluated and revised. The accepted forms have been provided for all participating laboratories to use in reporting the results of their trial runs of the Test.

3) Tests are being run on selected classes of blood samples routinely submitted to the laboratories on both known cancer cases and persons believed not to have cancer. Tests are also being run on some groups of general hospital admissions.

c. Major Findings

1) None to date. Collection of data in this evaluation is just beginning.

NCI-113
SERIAL NO.

PROJECT REPORT FORM (CONT'D)

d. Significance to Cancer Research

1) If a test can be developed that will reliably indicate which persons have a cancer of some site, by use of general screening techniques the regment of the populace in need of cancer diagnosis and treatment can be identified.

2) Present cancer case finding methods require much diffusion of effort and funds on screening by modified but time consuming physical and x-ray examinations. Successful development of a simple blood test for case detection will permit concentration on cancer diagnosis and treatment in individuals.

e. Proposed course of Project

Accummulation of Penn Test results and comparison of the test results with present and subsequent medical cancer history of the tested individuals.

PROJECT REPORT FORM (Cont'd)

10. NCI-113
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 8,779	1	0	1	1	0	1	0
FY 1956	$ 9,455	1	0	1	1	0	1	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Cooperating hospitals & laboratories selected by the California Study Group.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branc
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. St. Louis, Missouri.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-114
SERIAL NO

6. Prevalence of Gastric Achlorhydria in Selected Population Groups.
PROJECT TITLE

7. Dr. M. Sievers
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives.

1) Estimation of the prevalence of gastric achlorhydria in selected adult population groups using a newly developed technique of tubeless gastric analysis.

2) Determination of the usefulness and practicability of the new gastric analysis technique in multiphasic or single phasic health screening of population groups.

3) Evaluation of possible correlation between occurrence of gastric achlorhydria and of gastric cancer.

(B) Methods.

1) Simultaneous testing (on a clinical trial basis) of the orthodox and of the tubeless technique for gastric analysis on patients with known gastric disease, with known gastric cancer and on presumed normal control patients.

2) Performance of mass population screening using the tubeless gastric analysis technique.

3) Performance of tubeless gastric analysis on all patients receiving gastro-intestinal, x-ray examinations in selected hospital clinics.

(C) Major Findings.

None, yet. This project was begun in the final months of calendar year 1954.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM

(D) Significance to Cancer Research.
For years it has been thought that gastric achlordydria and gastric cancer show a high degree of correlation. Few data are available as to the probable prevalence of gastric achlorhydria in the general population. Application of the technique of tubeless gastric analysis will permit assay of achlorhydria occurrence in selected population groups. If there is positive correlation between achlorhydria and occurrence of gastric cancer, this test may prove to be a mass screening technique for identifying the individuals most apt to have or to develop gastric cancer.

(E) Proposed Course of Project.

1) Clinical trials to perfect skill and reliability in performing the tubeless gastric analysis.

2) Investigation of the oral use of gastric secretory stimulants for confirmation of test findings.

3) Conduct of screening in several industrial population groups and follow-up of the groups for occurrence of gastric cancer over the years.

4) Conduct of tubeless gastric analysis on hospital and clinic patients scheduled for orthodox gastric analysis and/or for gastrointestinal x-ray examination.

PROJECT REPORT FORM (Cont'd)

10. NCI-114
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 2926	1	0	1	1/3	0	1/3	
FY 1956	$ 4,727	1	0	1	1/2	0	1/2	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. St. Louis, Missouri
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-115
SERIAL NO.

6. Survivor Rates in a Selected Group of Treated Gastric Cancer Patients.
PROJECT TITLE

7. Dr. M. Sievers
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives.

1) Evaluation of factors common to 5 year survivors of treated gastric cancer that might bear on their survival.

2) Evaluation of factors in gastric cancer patients that may be pertinent to prognosis of their disease.

3) Collation of data on gastric cancer and duodenal ulcer looking for possible positive or negative correlation factors.

(B) Methods Employed

1) Review and abstract of clinical and hospital charts of all admissions to a large midwestern hospital for gastric malignancy during the past decade.

2) Current follow-up on all patients of the group to determine their survivorship and ultimate fate through personal contacts with patients or their relatives, through the hospital social service department and through visits to the hospital cancer clinic by the patient.

3) Search of vital records of appropriate communities for death certificates on patients known to be or suspected of being deceased.

4) Collation and biometric analysis of all data collected on the study group.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-115
SERIAL NO.

PROJECT REPORT FORM

9. PROJECT DESCRIPTION.

(C) Major Findings.

1) None. This project was started during the third quarter of calendar year 1954 and insufficient data is yet available to permit of reliable statistical analysis.

(D) Significance to Cancer Research.

1) Little statistically tested information is available relative to the factors bearing on survivorship in diagnosed, treated gastric cancer. This study offers promise of providing some of these data.

(E) Proposed Course of the Project.

1) The hospital charts and other sources of information on gastric cancer patients is to be examined looking for factors common to 5 year survivors such as similarities in blood type, or items related to age, sex, race, religion, marital status, etc.

2) Collected data will be subjected to statistical analysis and other scrutiny as may appear desirable in attaining the listed objectives of the project.

NCI-115
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

10. NCI-115
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 2926	1	0	1	1/3	0	1/3	0
FY 1956	$ 4,727	1	0	1	1/2	0	1/2	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Boston, Mass.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-116
SERIAL NO

6. Environmental exposures, during pregnancy, of mothers of infants developing cancer.
PROJECT TITLE

7. M. Manning
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objective

1) To determine possible environmental factors or facts related to family history, past medical history, or personal history of mothers of infants developing cancer, that may have contributed to, caused or precipitated occurrence of the cancer.

b. Methods Employed

1) This study began as an investigation of possible environmental cancer of cancer in infants. Experience during 1954 has made it desirable to expand the study to consider all types of cancer in infants.

2) Medical and hospital records of infants diagnosed in selected hospitals in New England as having cancer are reviewed.

3) Families of these cancer patients are interviewed with regard to maternal environmental exposures, and family and personal medical history. Particular attention is paid to history of radiation exposure and allergic disease.

4) Data for all patients and families in the study are collated in search for factors common to appreciable numbers of the cases.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION (continued)

c. Major Findings

1) In the sample population studied to date approximately 40% show positive maternal history of allergy. Virus infections also appeared suggestively increased as did therapeutic blood transfusions.

d. Significance to Cancer Research

1) This study was undertaken in attempt to discover possible maternal environmental causes for leukemia in infancy. Incomplete results so far indicate a definite desirability for looking into these factors as a possible cause for occurrence of certain other cancers in infants.

2) Findings of this project may well contribute to solution of the cause of leukemias and certain other cancers in children and adults.

e. Proposed Course of the Project

1) Continued collection of case, maternal and family data on infants who are diagnosed in the cooperating hospitals as having cancer.

2) Collation and biometric analysis of data collected in search of factors common to the cases and persons comprising the study group.

PROJECT REPORT FORM (Cont'd)

10. NCI-116
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 5,857	1	0	1	2/3	0	2/3	0
FY 1956	$ 4,727	1	0	1	1/2	0	1/2	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Children's Hospital, Boston, Mass

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations & Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Boston, Massachusetts
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-117
SERIAL NO

6. Leukemia Occurrence in ~~a~~ Selected New England States
PROJECT TITLE

7. Dr. Miriam Manning
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

1) To search for environmental, familial or personal medical history factors common to leukemia cases diagnosed and reported in a selected state.

b. Methods Employed

1) This study is an outgrowth of another study of leukemic infants, their parents and families in which preliminary data point toward maternal environmental and medical history factors in the cause or presipitation of the leukemic state.

2) Statistics are being obtained on the occurrence of and mortality from leukemia in all age groups in the study state. Geographical locations of the reported cases will be reviewed and, as practicable, patients and families will be interviewed for information on environment, medical history, family history and occupational history. Emphasis, presently, is on radiation exposure and allergic disease.

c. Major Findings

1) None. This study was started in the final quarter of the calendar year 1954.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

CI-117
ERIAL NO.

d. Significance to Cancer Research

1) If the collateral data on leukemia in infants is even partially borne out through this investigation, a suspected correlation between environmental factors or disease factors (such as allergy) in causing leukemia may be confirmed.

2) This study will also serve as a possible control for the study of maternal influence on occurrence of cancer in infants.

3) In company with the study of maternal influence on occurrence of cancer in infants, this project can seek differences in etiology of leukemia in adults and in infants.

e. Proposed Course of Project

1) Collection and collation of leukemia morbidity and mortality data through cooperation of the vital statistics service, and selected hospitals and practicing physicians in the selected state.

PROJECT REPORT FORM (Cont'd)

10. NCl-117
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$2,926	1	0	1	1/3	0	1/3	
FY 1956	$4,727	1	0	1	1/2	0	1/2	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Mass. State Health Department

New Hampshire State Health Department

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch and Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Field Studies Section and Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-118
SERIAL NO

6. Geographical Incidence of Cancer of Major Sites in Upstate New York
PROJECT TITLE

7. Dr. R. Taylor, B. Carroll
PRINCIPAL INVESTIGATOR(S)

8. Pope Lawrence
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives.

1) To study the geographical pattern of cancer incidence for selected sites in Upstate New York.

2) To relate the findings to data from other studies of incidence and mortality.

(B) Methods Employed.

1) The New York State Department of Health has made available its punch cards for reported cancer cases for the years 1949 - 1951. The data are believed to be unusually complete and accurate. These will be analyzed by county, city, and Statewide urban-rural groupings, using the indirect method of adjustment for age, sex, and urban-rural residence. A deck of 1950 New York Population cards was purchased from the Bureau of the Census to furnish the population bases for computing rates.

(C) Major Findings.

1) Age-specific incidence rates have been computed by sex and residence for nine major cancer site groups and 10 specific cancer sites. The next stage in adjustment of rates is in progress.

(D) Significance to Cancer Research.

1) There is a need for systematic compilation of geographical variations in incidence and mortality in order to learn of any patterns which may emerge. Hypotheses as to cancerigenic factors often imply characteristic geographical distributions which can be verified or refuted by analyses of this kind.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-118
SERIAL NO.

9. PROJECT DESCRIPTION (continued)

(E) Proposed Course of Project.

1) It is expected that the analysis will be completed during calendar year 1955. The type and nature of follow-up studies, if any, will depend on the findings.

PROJECT REPORT FORM (Cont'd)

10. NCI-118
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 4,389	2	0	2	1/2	0	1/2	0
FY 1956	$ 3,152	2	0	2	1/3	0	1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

New York State Department of Health (may not be called on in 1955 or 1956).

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Boston, Mass.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-119
SERIAL NO

6. Cancer Mortality in several selected population groups in New England
PROJECT TITLE

7. R. Taylor
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

1) Evaluation of cancer occurrence rates in selected population groups living carefully supervised and regulated lives.

2) Comparison of cancer rates in the study population with those in the general population.

b. Methods Employed

1) Names and identifying data are obtained on members comprising the study group (aggregating approximately 6000 persons) and pertinent data on environment, personal medical history, etc., are tabulated.

2) Vital records of the appropriate communities are searched for death certificates on deceased members of the group. The study includes individuals dying as early as 1875 and as late as 1954.

3) Appropriate tabulation, collation and biometric analysis is made of the data to discover similarities to and differences from similar data relative to the general population as corrected for age and sex distribution of the study group.

c. Major Findings

1) None. This study is expected to be completed and an appropriate report prepared during calendar year 1955.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION (continued)

d. Significance to Cancer Research

1) Considerable information is available covering cancer occurrence in the general population and many occupational groups. Little is known about cancer in the supervised and regulated population groups, certain of which are typified by this study group. The comparison made possible by this study may well help uncover items in cancer etiology previously obscured by the relative homogeniety of the general population.

e. Proposed Course of the Project

1) The personal identifying data has been obtained.

2) Search for pertinent death certificates for deaths from all causes is being conducted and copies of the certificates are being obtained.

3) As soon as information on all 6000 persons is obtained appropriate collation and statistical inspection of the information will be accomplished.

PROJECT REPORT FORM (Cont'd)

10. NCI-119
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$585	1	0	1	2/3	0	2/3	0
FY 1956	$5,1[illegible]	1	0	1	1/3	0	1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐
ADMINISTRATION ☐
REVIEW & APPROVAL ☐
TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch & Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Field Studies Section &/ Biometry Section
SECTION OR SERVICE

4. Bethesda, Md., & Chicago, Ill.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-120
SERIAL NO

6. Cancer as a cause of death and disability in railroad workers
PROJECT TITLE

7. S. Ingraham, B. Carroll
PRINCIPAL INVESTIGATOR(S)

8. P. Lawrence
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

1) To determine occupational and other group differentials in mortality and disability from cancer of various sites (with particular attention to the lung) among employees in the railroad industry.

2) To make comparisons with figures for the general population. Any similarities or differences found can serve as leads for detailed investigations as to specific etiological factors (possibly in cooperation with railroad medical departments)

b. Methods Employed

1) A cohort of all railroad employees with at least 10 years of service, either active in 1951 or retired by the end of 1951, is being set up. It numbers about 1,000,000 persons. Data for this cohort covering mortality from all causes and disability due to cancer is being assembled at RRB headquarters from punch-card files and from claims. The desired data are being supplied to the Institute in the form of duplicate punch cards, tabulations and claim data representing the defined cohort and the deaths and disabilities among its members in 1952. The same cohort can be followed for succeeding years if desired. Data will be available to classify members of cohort and cancer cases as to age, sex, length of service, occupation, and employer for making both gross and detailed comparisons. Since all causes of death are being taken into account in coding, data will be available of interest to other institutes. The Heart Institute has already undertaken to pay part of the cost of this project in return for tabulations of deaths from cardiovascular disease.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-120
SERIAL NO.

9. PROJECT DESCRIPTION (continued)

c. Findings

1) None as yet. Selection of cases and transcription of claim data are now going forward in Chicago.

d. Significance to Cancer Research

1) Railroad employees constitute an occupationally stable group with their own retirement system. This is an ideal setting in which to attempt investigation of occupational factors and will provide good experience for later handling occupational data collected in Social Security Board operations. Certain railroad employees are known to be exposed to carcinogenic agents and we have here a direct means of observing the effects. With a defined cohort, holding certain occupational factors constant, it would be possible to supplement the RRB records with collection of additional details on personal histories (in cooperation with individual railroads) to test association with other factors.

e. Proposed Course of the Project

1) The first year has been the working out of operational details of collecting the data and the partial compilation of cohort and cancer data. Complete data for the first year should be received and analyzed during calendar year 1955, which will determine the scope and detail of tabulations for succeeding years.

PROJECT REPORT FORM (Cont'd)

10. NCI-12
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$2,926	2	0	2	1/3	0	1/3	0
FY 1956	$5,152	2	0	2	1/3	0	1/3	0

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12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

National Heart Institute
National Office of Vital Statistics
Railroad Retirement Board

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations & Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Atlanta, Georgia
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-121
SERIAL NO

6. Oral Cancer in Relation to Vitamin Deficiency and/or Use of Snuff
PROJECT TITLE

7. Dr. Samuel C. Ingraham, II
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

1) To seek possible relationships between occurrence of oral or pharyngial cancer and vitamin deficiencies and/or the use of snuff (pulverized tobacco)

b. Methods employed

1) Review of pertinent hospital records in selected hospitals at Atlanta, Georgia for cases of diagnosed cancer of the oropharyngeal area.

2) Abstract and collation of appropriate data, from records of the cancer cases and interview of the patients, in search for factors common to groups of the study population.

c. Major Findings

1) Approximately 15% of patients with cancer of the orophagus had vitaminosis.

2) 70% of the women with cancer of the buccal mucosa had been snuff dippers.

3) 40% of patients with cancer of the tongue were women (apparently there was no relationship in this group to use of snuff).

4) The ratio of women with cancer of the buccal mucosa to men with cancer of the same area is 1:1.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

d. Significance to Cancer Research

1) This investigation, as far as it proceeded, hints at a specific relationship between use of snuff and/or avitaminosis and the occurrence of cancer of the upper gastrointestinal tract.

e. Proposed Course of the Project

1) Because of resignation of the Medical Officer who was conducting this study, it is being held in abeyance for the present. The records and biometric analysis of data gathered have been turned over to a physician in Atlanta known to both the cooperating hospitals and the Field Studies Section. When a replacement for the Medical Officer is obtained, the study will be reactivated.

PROJECT REPORT FORM (Cont'd)

10. NCI-121
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	0	1	0	1	0	0	0	0
FY 1956	0	1	0	1	0	0	0	0

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12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch and Division of Special Health Services
LABORATORY OR BRANCH

3. Occupational Health Program Field Studies Section and
SECTION OR SERVICE

4. Salt Lake City, Utah.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-122
SERIAL NO

6. Effects of Elevated Levels of Radon on Miners in Montana, Idaho, Colorado, Utah and New Mexico.
PROJECT TITLE

7. Dr. J. Egan, P. A. Lawrence
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives.

1) To evaluate the prevalence of cancer of the lung among underground non-uranium miners in the Rocky Mountain Area.

(B) Methods Employed.

1) Assembly of occupational, medical and vital statistics information on a composite group of hard-rock miners with at least 5 years of underground working experience in non-uranium mines in the Rocky Mountain States.

2) Collation and medical statistical analysis of the collected data with particular emphasis on lung cancer cases and deaths that may be discovered.

3) This selected population will be followed for several years by appropriate case-finding and follow-up methods for several years to determine the incidence and prevalence of cancer in the group.

4) Collection of environmental data with respect to underground radon concentrations in the selected non-uranium miner is being done by the Occupational Health Program Field Station in Salt Lake City in cooperation with the State Health Departments of Colorado, Utah and New Mexico.

(C) Major Findings.

1) It has been established that radon concentration in the air of many of the hard-rock mines in the Rocky Mountain Area appreciably exceed the Maximum Permissible Concentration recommended by the National Committee on Radiation Protection.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION.

(C) Major Findings (Continued)

2) There are no medical findings to date: Negotiations are still under way with several of the large mining companies in the Rocky Mountain Area to obtain their cooperation by making payroll lists, addresses and medical examination records of their hard-rock miners available for abstract study..

3) It has been ascertained that, once names and identifying data on the miners are available, the vital statistics and other necessary sections of the several States concerned will cooperate by making available pertinent data or vital records in their possession.

(D) Significance to Cancer Research.

Data on human beings exposed to a potentially carcinogenic, radioactive environment will be compiled and so becomes available for possible use in cancer control. At present such information is extremely scarce. Limited studies of mining communities in Europe have revealed high incidence of lung cancer in miners working in Pitchblend mines. Extensive animal experiments in Europe and the Americas as well as observations made on human beings inadvertantly exposed to excessive radiation over prolonged periods of time have established beyond doubt that ionizing radiation causes cancers in animals and in people.

(E) Proposed Course of Project.

1) Negotiations are almost completed with several large mining companies to make their personnel and medical records on miners available for abstracting, coding and necessary follow-up. Insistance is on maintaining anonymity of individuals and companies.

2) As soon as the identifying data is made available by the mining companies, plans for collating current data will be executed and plans for following individual miners over a period of years will be initiated. States vital statistics sections and others have promised cooperation in making available vital records and in aiding with tracing of miners who may have moved or transferred to other companies or industries.

3) Analysis of data is to be done under guidance of the office of Biometry of the National Institutes of Health.

4) A more exact time-table for this project must await favorable action by the several mining companies.

PROJECT REPORT FORM (Cont'd)

10. NCI-122
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,389	2	0	2	1/2	0	1/2	0
FY 1956	$4,727	2	0	2	1/2	0	1/2	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations & Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Salt Lake City, Utah
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-123
SERIAL NO

6. Comparative Study of Lung and Bowel cancer in relation to occupation.
PROJECT TITLE

7. J. Egan
PRINCIPAL INVESTIGATOR(S)

8. S. Ingraham
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

1) To look for possible occupational similarities in victims of lung cancer or cancer of the large bowel.

2) To evaluate possible environmental factors in cause or occurrnce of cancer of the lung.

b. Methods Employed

1) Most hospitals in Utah and Western Colorado are cooperating in this project by having as complete occupational and environmental exposure histories as practicable taken on all cases of lung or bowel cancer admitted.

2) Data on all the cases will be examined, collated and otherwise analyzed biostatistically in search of factors possible common to the personal and working histories of the patients.

c. Major Findings

1) None. This study was started in the final quarter of calendar year 1954.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-123
SERIAL NO.

PROJECT REPORT FORM (CONT'D)

d. Significance to Cancer Research

1) This study is expected to make available specific information relative to the interrelationship of lung cancer or bowel cancer and the environment. It currently is suspected that environmental carcinogens play a significant role in occurrence of lung cancer and possibly also of cancer of the large bowel.

e. Proposed Course of the Project

1) Occupational and environmental histories will be collected on most hospital admissions for lung or bowel cancer in the cooperating hospitals,

2) The data collected will be examined for statistically significant trends.

PROJECT REPORT FORM (Cont'd)

10. NCI-123
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$2926	2	0	2	1/3	0	1/3	0
FY 1956	$3,152	2	0	2	1/3	0	1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

(1) Hospitals in Utah and Western Colorado.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
Division of Special Health Services
LABORATORY OR BRANCH

3. Field Studies Section &
Occupational Health Program
SECTION OR SERVICE

4. Salt Lake City, Utah.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-124
SERIAL NC

6. Medical Study of the Uranium Miners on the Colorado Plateau
PROJECT TITLE

7. J. Egan, P. Lawrence
PRINCIPAL INVESTIGATOR(S)

8. S. Ingraham, D. Holladay
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

1) To examine, as nearly as possible, the entire population of the uranium mining industry.

2) To compile a census of examinees and other uranium miners for future, year-to-year follow-up with special reference to lung cancer (10-12 year planned).

3) To determine the frequency of cancer of the respiratory system, skin, bone, and leukemia in persons employed in underground uranium mining operations.

b. Methods Employed.

1) From records of the Atomic Energy Commission and of the States of Utah, Colorado, New Mexico and Arizona, a census of uranium mines and their locations was obtained.

2) During summer, 1954, two medical examining teams, housed in trailers, visited a series of locations on the Colorado Plateau Area and examined approximately 1400 Uranium miners who volunteered for the "base-line" examination.

3) Name, address and other follow-up information was gathered on all uranium miners who could be contacted regardless of whether or not they were examined.

4) Medical examinations included patient's history, a physical examination, chest x-ray, blood studies, and urinalysis.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION (continued)

5) Probable exposures to radon and the radiations from uranium ore will be estimated from physical radiation measurements taken in the several mines and made on air samples collected in the several mines.

6) Follow-up of individual miners will be aided by lists of names and employers made available from State Offices of Internal Revenue, by lists of names and addresses from State Automobile License Bureau, by assistance of local postmasters, etc.

7) For notice of deaths among the study group, all local newspapers will be scanned continually, state and large city vital statistics sections will make available files of death certificates and personal inquiry will be made at least annually at the time of the study census.

c. Major Findings

1) None. It is expected that this study will last at least 10 years. Annual or possibly semi-annual report of the miners census should be made and periodic report of the physical examinations will be necessary. Appropriate funds for these activities should be included in budget planning.

d. Significance to Cancer Research

1) Published information on pitchblend miners in Europe indicates a lung cancer occurrence of more than 50% in the group.

2) Radiation exposure of prolonged, low intensity is suspected of being a carcinogen in human beings.

3) Study of the uranium miners in the Colorado Plateau area is expected to furnish needed information for protection of uranium miners and may also supply data pertinent to carcinogenic effects of naturally occurring ionizing radiations.

e. Proposed Course of Project

1) Approximately 1400 miners comprise the present study group. It is estimated that from 700 to 1000 additional uranium miners are in the Colorado Plateau Area. As is practicable, attempt will be made to add this latter group to the study population.

2) From fiscal year 1950 through fiscal year 1953, approximately 1200 uranium miners and millers had been examined by physicians assigned to the Division of Occupational Health. Reviews of these records indicated that:

(a) In 1951 there were only three or four repeat examinations of the 1950 examinees.

(b) In 1953 only 12 people examined had had more than 10 years experience in the uranium mines, approximately 80% of the examinees had less than 3 years in the uranium mines, and there were approximately 68 re-examinations.

(c) Except by intensive survey-medical examination approach it would be most difficult to locate even as many as 500 people over 30 years of age with more than 3 years of uranium mining experience.

9. PROJECT DESCRIPTION (continued)

3) Because of the increasing importance of uranium mining as an occupation, because of the increased cancer incidence in European pitchblend mines, and because of the demonstrated difficulty in following uranium miners for even a year or so, need was recognized for a specific, continuing project-type study of uranium miners in the United States.

4) Summer of 1954 was used to contact miners, obtain baseline physical examinations on them and to develop a census with sufficient personal identifying information that the chance of prolonged follow-up of the miners is practicable.

5) Presently the information collected last summer is being examined, organized and collated. Census lists and files are being compiled, and attempt is being made to contact the individual miners to report to them the findings of their medical examination; and, indicentally, to check on their whereabouts. Also, for those men found to be in need of further medical study and treatment, recommendation to that effect is being made to the men and to their physicians.

6) In calendar year 1955 an intensive effort will be made to recontact each miner and to account for all who cannot be personally contacted.

7) As statistical data about the uranium mines and the miners and their cancer rates accumulate, they will be analyzed biometrically and examined for information pertinent to radiation and its carcinogenic effects on human beings.

8) Success of this project depends upon the acquisition of future annual census data and death record data, to reveal those individuals who disappear from the original "population group"in order that they may be traced and their fates determined.

PROJECT REPORT FORM (Cont'd)

10. NCI-124
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 52,101	11	3	14	5	2	7	0
FY 1956	$ 19,013	4	5	9	1	2	3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

a. Atomic Energy Commission
b. Occupational Health Program, Division of Special Health Services, PHS
c. Tuberculosis Program, Division of Special Health Services, PHS

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch and Office of Biometry
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Bethesda
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-125
SERIAL NO.

6. The Incidence of Respiratory Cancer and Other Major Diseases Among World War I Veterans in Relation to Their Smoking Habits.
PROJECT TITLE

7. H. F. Dorn, W. S. Baum
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objective.

To determine by direct observation of a defined cohort the mortality from respiratory cancer and other major diseases among male smokers and non-smokers in the age group of 50 and above.

(B) Methods.

It was determined that as of January 1954 over 300,000 World War I veterans had active insurance policies, covered by the insurance program of the Veterans Administration. The Veterans Administration distributed to all of these policy holders a detailed smoking questionnaire prepared by the National Cancer Institute. The questionnaire, containing detailed data on smoking habits and other pertinent data, were returned to the National Institutes of Health by the veteran policy holders. This data is coded at the National Institutes of Health, and as deaths occur among the cohort group, duplicate copies of the death certificates are furnished by the Veterans Administration to the study group at National Institutes of Health. In addition, letters are sent to the physicians and hospitals where the deaths occurred, so that more precise information may be obtained regarding the diagnosis, and the cause of death. This data when returned is coded on the history card for ultimate analysis.

(C) Major Findings.

The study has not progressed sufficiently far to permit an analysis of data obtained. It is felt that no report should be made, until sufficient data for valid observations is obtained. Over the course of the current calendar year over 200,000 smoking questionnaires have been returned, and are now in the process of coding. On the returns to date it is estimated that there

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT DESCRIPTION.

(C) Major Findings (Continued)

will be over 3,000 deaths in this group, on whom death certificates and additional mortality data by letter are being obtained for coding. It appears that there will be over 200 deaths from cancers of the respiratory tract in this group.

(D) Significance to Cancer Research.

The majority of data to date on the relation of respiratory cancer and smoking have been obtained from retrospective studies. One disturbing feature about these studies, is that taking these studies as a group, the relative risk for developing respiratory cancer among the heavy smokers varies within very wide limits. Thus, if there is a risk, it is not possible to assess the degree of risk present. The magnitude of risk ranges from 2 times to 80 times in this group of studies, thus indicating that further definitive data are necessary.

Two other forward looking studies on defined population groups are currently being conducted. It is believed that careful analysis of a large group is necessary to determine the magnitude of risk, if any, that exists among smokers and non-smokers in the development of respiratory cancer and other major diseases.

(E) Proposed Course of Project.

The project will continue in its present form, until coding is completed on approximately 7,000 deceased patients, including a group of approximately 500 patients with respiratory cancer. At that time detailed analysis will be attempted regarding the relationship to respiratory cancer, and information will continue to be collected as long as is necessary to determine the association between smoking and other major diseases.

PROJECT REPORT FORM (Cont'd)

10. NCI-125
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 11,132	1 ~~2 (1/3)~~	2 ~~5~~	3 ~~7~~	1/3	2	2 1/3	0
FY 1956	$ 12,710	1 ~~2 (1/3)~~	2 ~~5~~	3 ~~7~~	1/3	2	2 1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

This is a cooperative project between the Veterans Administration, and the Public Health Service represented by the Field Investigations and Demonstrations Branch of the National Cancer Institute, and the Office of Biometry of the National Institutes of Health.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No projects similar to this are being conducted elsewhere in the Public Health Service.

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch, and Office of Biometry
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Richmond, Va.
Durham, N.C., Reidsville, Va. and
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-126
SERIAL NO

6. The Occurrence of Cancer and Other Major Diseases Among Personnel Employed in the Manufacture of Cigarettes.
PROJECT TITLE

7. H. Dorn and W. Baum
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) The objective of this study is to determine the frequency of occurrence of cancer of the respiratory tract and of other major sites, and the frequency of occurrence of other major diseases among personnel engaged in the manufacture of cigarettes.

(B) Methods employed. Through the cooperation of one of the major tobacco manufacturers, a study was made of personnel and insurance records on employees over the period from 1946 through 1952. The cigarette industry in question had an insurance program whereby each worker who served for a period longer than a year was covered by insurance with death benefits. Consequently, a report of death was necessary on each employment for the benefits to be collected. The industry in question had over 20,000 employees, 12,000 of whom were engaged in the manufacture of cigarettes.

(C) Patient material. The population at risk consisted of the 12,000 cigarette workers under employ by the industry in question, for a period of 6 1/4 years. In addition to this group, corresponding data was obtained for all other employees in this industry not engaged in the manufacture of cigarettes, and the final results were compared to the State-wide analyses of mortality data.

(D) Major findings. Mortality rates based on deaths for the two years, 1949 and 1950, were computed by age, sex and color for the diseases in question, for the combined populations of the two States of Virginia and North Carolina. The age distribution of the employees engaged by the industry by sex and color was available for August 1, 1953, and the total number of employees by sex and color was available for each year of the study period. The number of person years exposure was 70,500. The number of deaths from cancer of the major sites, from cardiac disease, and from all causes was lower in these groups studied than the expected number, as based upon the mortality data from the States.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION. (Continued)

E) Significance of this Project. Literature in the past suggests (Seyfarth), that there is a greater risk for respiratory cancer among personnel engaged in the handling of tobacco. The data consist of pathological material, and do nothing more than suggest an association. Current controversy surrounds the question of the association of smoking of cigarettes and the rise of the respiratory cancer rate, and whether these are causally related. Such a study is of importance, since it should throw some light upon the effect of nicotine and tobacco alkaloids, and the effect of exposure to these materials upon the development of respiratory cancer and cardiac disease.

PROJECT REPORT FORM (Cont'd)

10. NCI-126
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	0	1 [illegible]	0 [illegible]	1 [illegible]	0	0	0	0
FY 1956	0	1	0	1	0	0	0	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

The American Tobacco Company cooperated in this project with the National Institutes of Health, represented by the Office of Biometry and the Field Investigations and Demonstrations Branch.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No other projects similar to this have been done or are being done by the Public Health Service.

PROJECT REPORT FORM (Cont'd)

15. NC1-126
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Report now prepared for publication.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Bethesda, Md.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-127
SERIAL NO

6. Frequency of Occurrence of Lung Cancer Among Selected Occupational Groups of Civil Service Personnel.
PROJECT TITLE

7. W. S. Baum and N. B. Hon
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives.
To determine the frequency of occurrence of respiratory cancer among selected groups of civil service personnel. With this data on hand, leads for further investigation of the occurrence of environmental cancers would be followed-up.

(B) Methods employed.
The Civil Service Commission, because of retirement benefits, maintains complete files of medical diagnoses on personnel employed by this Commission. All cases of respiratory cancer listed, who had expired from this disease, were studied to obtain information on identifying number, address, sex, age, date of death, diagnosis, confirmation of diagnosis, place of death, length of service, and a complete occupational history. This information had already been tabulated for insurance purposes, and by bringing it together, valuable leads for environmental cancer studies might be obtained. Consequently, abstracts were made on 231 records of patients who had expired from respiratory cancer, and abstracts were made on 55 disability cases who had been treated for cancer of the respiratory tract. The majority of these deaths had occurred within the past three to four years.

(C) Major findings.
Preliminary results indicate ~~that~~ on the majority of the cases there is a high percentage of microscopic confirmation of the diagnosis. Also, while a portion of the cases dates back for a period of 40 years, in many the occupational history commenced around 1940. Because of this it was felt that after analysis, more occupational history should be obtained if possible with the cooperation of the Civil Service Commission.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION (Continued).

(D) Significance to cancer research.
Incidence rates on the occurrence of respiratory cancer among selected occupational groups are virtually nonexistant. This study, if the mechanism for the obtaining of incidence rates could be set up in a department where the information is collected for other reasons, would provide an excellent source of information to further the studies now being undertaken in the etiologies of environmental cancer.

(E) Proposed course of project.
It is planned to complete the analysis, and on the data obtained to date to show the frequency of occurrence of respiratory cancer among the occupational groups listed. Following this, further conferences will be held with the Civil Service Commission in regard to the following two points. 1. The obtaining of additional occupational history on those patients who have expired. 2. The maintaining of a current file, so that this information may be collected from year to year.

It is important to remember that in these records no individuals are identified, the records are identified by number only, and except for general results the study is a confidential one in which no information about any designated person would be available to any person outside of the study group.

PROJECT REPORT FORM (Cont'd)

10. NCI-127
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 14,441	2	1	3	1 1/3	2/3	2	0
FY 1956	$ 6,338	2	1	3	1/3	2/3	1	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This project resembles the study in Providence on data obtained from the State Unemployment Commission by Dr. John Vander. This study, however, is entirely retrospective, while Dr. Vander's study is forward-looking, since complete occupational histories will be taken from patients who have developed lung cancer. The two studies, however, might complement each other in obtaining leads for further investigation of potential environmental causes of cancer.

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Cleveland, Ohio and Washington, D.C.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-128
SERIAL NO

6. Cancer Among Railroad Workers in Certain Occupations.
PROJECT TITLE

7. P. Lawrence, B. Carroll
PRINCIPAL INVESTIGATOR(S)

8. Dr. S. Ingraham.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives

1) To study age and occupational patterns of cancer mortality among a particular segment of railroad employees;

2) To test the feasibility of obtaining the necessary data from the files of two brotherhoods with a view to securing more detailed information in future years through changes in record requirements and procedures on the part of the brotherhoods. It is hoped that data can thus be obtained on such aspects as confirmation of diagnosis, histologic type, etc.

(B) Methods Employed.

1) Data have been obtained from the Insurance Department records of the Brotherhood of Railway Trainmen and the Brotherhood of Locomotive Firemen and Enginemen covering age, length of membership, and local lodge affiliation of all members carryihg life insurance, and corresponding data for all insured members dying from 1950 through 1953. Each case will be looked up in death certificate files at NOVS to determine cause of death for analysis according to the variables indicated. If this procedure proves productive and economical, proposals will be formulated for additional reporting and record provisions on the part of the brotherhoods in order to obtain the more detailed types of information mentioned above under (A).

(C) Findings.

1) None as yet. The data have been punched into cards which are being processed in preparation for looking up cause of death in NOVS files.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION

(D) Significance to Cancer Research.

1) While this study is, in its first stage, similar to the Railroad Retirement Board study, its real significance lies in the prospect of obtaining valuable medical data in future years. This information would cover, for each cancer death, such items as confirmation of diagnosis and histologic type of tumor. The analysis of these data in connection with occupational or regional variations in cancer mortality, as revealed in this or the Railroad Retirement Board study, would add considerably to our understanding of these variations in relation to possible occupational carcinogens.

(E) Proposed Course of Project.

1) Calendar year 1955 should see the completion of the first stage, namely, analysis of the data obtained from existing records. If indications are favorable, steps may also be taken during the year to arrange for collection of additional data during future years.

PROJECT REPORT FORM (Cont'd)

10. NCI-128
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 5,851	2	0	2	2/3	0	2/3	0
FY 1956	$ 6,303	2	0	2	2/3	0	2/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☑

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Brotherhood of Railroad Trainmen
Brotherhood of Locomotive Firemen and Enginemen
National Office of Vital Statistics
Canadian Provincial Offices of Vital Statistics

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. National Cancer — INSTITUTE

2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH

3. Field Studies Section — SECTION OR SERVICE

4. Oklahoma City, Oklahoma — LOCATION (IF OTHER THAN BETHESDA)

5. NCI-129 — SERIAL NO

6. Health Survey of personnel employed in baths at Hot Springs, Arkansas — PROJECT TITLE

7. P. Morgan and P. A. Lawrence — PRINCIPAL INVESTIGATOR(S)

8. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objective

(1) To evaluate the cancer experience in a selected occupational group with long-time exposure to increased atmospheric concentrations of radon and its decoy products.

b. Methods Employed: This project combines a retrospective and a forward-looking field investigation.

(1) The population group for the forward-looking study includes all employees of 18 bath houses in Hot Springs, Arkansas. These people are under supervision of the National Park Service. They receive periodic and annual physical examination under auspices of the Public Health Service. Each employee has been interviewed for pertinent personal and occupational data including reproductive history, medical history and personal habits (smoking, etc.). Attempt will be made to follow this group to death.

(2) The population for the combined retrospective-forward-looking study is restricted to the massage operators who have been employed since 1936. All those having left employment are being traced by social security number, postal forwarding system and otherwise. All but 6 are now accounted for.

c. Major findings:

(1) Record search confirmed original rumor that 6 massage operators of

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

the active group did, indeed, die of cancer within an 18 month period. Also two cases of leukemia have occurred so far. Because of the size and age distribution of the study group it is not yet possible to assess the significance of the facts.

(2) Environmental data collected so far reveal that these people work in an atmospheric concentration of radon considerably in excess of the maximum permissible concentration recommended by the National Committee on Radiation Protection. A collateral, surprising development is the discovery that at several locations in the community in which these operators live the atmospheric radon concentration is even higher than at their place of work.

(3) Pertinent data from physical examination records of the group include:

(a) 120 of the first 299 charts reviewed showed increased sedimentation rates.

(b) 36 of the first 299 cases had some degree of hypertension (most showed in excess of 160/100 millimeters of mercury).

(c) 61 of the first 299 cases had some increase in percentile count of lymphocytes in the differential white blood cell count; several cases had reversal of the usual polymorphonuclear/lumphocyte ratio. These cases had sufficiently increased white blood cell count to warrant further medical study.

(d) Thyroid enlargement was noted in 18 of the first 299 case records reviewed. One patient had a thyroidectomy.

(d) Significance to cancer research

Insofaras field investigations into etiology of cancer is concerned, this project seems ideal in that it is a naturally-occurring field experiment that was awaiting investigation. It affords an opportunity to study the effects of exposure of human beings to increased and probably constant levels of naturally occurring radon and its decoy products. Laboratory experiments with animals have shown that these radioactive substances are carcinogenic.

The experiment is uncomplicated by such factors as heavy industrial air pollution or the handling of a multiplicity of suspected carcinogens as are found in other occupational environments. Results obtained will have important bearing on other researches in the field of low-level exposure to radioactive substances.

(e) Proposed course of this project:

(1) In February 1955 all active bath house personnel will receive another comprehensive physical examination by a contract physician in a contract hospital. These data will be added to the study records.

(2) All massage workers will be contacted again in 1955 to ascertain their health status.

(3) Continuing efforts will be made to discover information about the person yet missing from the study.

(4) Additional environmental data will be collected.

PROJECT REPORT FORM (Cont'd)

10. NCI-129
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$2,926	2	0	2	1/3	0	1/3	0
FY 1956	$ 3,152	2	0	2	1/3	0	1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Federal Park Service.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations & Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-130
SERIAL NO

6. Survey of Cancer Mortality in West Virginia
PROJECT TITLE

7. P.A. Lawrence, Ruth Taylor
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

a. Objectives

1) To determine any significant differences in the distribution of cancer mortality rates between the counties in a single, selected state and to search for possible reasons for any observed differences.

b. Methods Employed

1) Review and collection of vital statistics records for cancer deaths occurring over a 12 year period. Classification, grouping, enumeration of the data and computation of various rates adjusted for such factors as age, sex, race and occupation is being done.

2) In the counties showing significantly different (high or low) rates for specific cancer sites, more detailed study will be planned of such local factors on industry, topography, air pollution, and characteristics and habits of the population.

3) Leads developed by study of local factors will be followed further by the direct approach to suspected sources of potential carcinogens. Detailed inquiry among small, selected population groups will be exploited with resepct to cancer experience and environment.

c. Major Findings

1) One set of data covering cancer deaths for all sites for 1946-1947

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

indicates a higher than expected occurrence of primary cancer of the liver and biliary system.

2) Another set of data covering all deaths from cancer of the lung for the period 1940-1951 inclusive showed statistically significant differences in rates between counties.

3) A third set of data covering all lung cancer deaths among West Virginia residents (including those who died out of state) in 10 years yielded 8 counties with rates sufficiently high to be worthy of specific investigation.

4) Occupational classification of death certificates for the 12 year study period reconfirmed an impression that lung cancer seems to occur with increased frequency in persons working with metals.

5) Because of precedence in urgency of other projects, further work on this project is being held in abeyance. However, all basic data have been collected, tabulated and studied to some extent.

d. Significance to Cancer Research

1) Nickel is a suspected carcinogen and West Virginia contains the only major nickel refinery in the United States.

2) The county in which the refinery is located did show a significantly higher lung cancer rate than the rest of the state. Death certificate data are insufficient to even suggest that the nickel plant may be responsible for the increased cancer deaths: -- other factors can be explored only on a local level.

3) More reliable information on cancer incidence in general and on lung cancer in particular are needed to help detect the environmental factors which may be related to its cause. Similar state-wide cancer mortality studies in the United States have been published but they have usually been confined to shorter base periods (5 years or less). The present 10-12 year study should yield more stable statistical information.

e. Proposed Course of Project

1) As soon as personnel time allows, a report of this statistical study is to be prepared. Based on the report, appropriate local investigations will be planned in individual counties or other subdivisions to pursue further any possible environmental causes of increased or decreased cancer rates. It is believed that possible carcinogenic factors can be explored only on a local project basis.

PROJECT REPORT FORM (Cont'd)

10. NCI-130
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 2,926	2	0	2	1/3	0	1/3	
FY 1956	$ 3,152	2	0	2	1/3	0	1/3	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

West Virginia State Department of Health.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branc
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-13
SERIAL NO

6. Geographic Distribution of Respiratory Cancer Mortality in 15 Selected States.
PROJECT TITLE

7. P. Lawrence, F. Young.
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives.

1) To discover geographic locations of any areas within fifteen selected States which might be experiencing unusual mortality rates due to pulmonary cancer.

(B) Methods Employed.

1) Special tabulations covering a ten-year period were obtained from the National Office of Vital Statistics. Analysis will be made of all cancer deaths due to oral and pulmonary cancer occurring among residents of the selected States by year, county, race, sex, and age. The States included are: West Virginia, Virginia, Maryland, Pennsylvania, Ohio, Kentucky, and North Carolina; Missouri, Arkansas, and Louisiana; Arizona, Utah, Colorado, New Mexico, and Montana.

2) Computations to be made include age-specific rates by State, county, site, sex, and race. Age-adjusted rates will be computed for interstate and inter-regional comparison. Ratios of observed to expected cases based on State rates will be used for intra-State comparisons by county. Standard tests for significance of differences will be applied in cooperation with the Biometrics Section of National Cancer Institute.

(C) Major Findings.

No major findings at this time. However, some interesting and statistically significant geographical differences are developing.

(D) Significance to Cancer Research.

1) With full realization of the shortcomings of cancer mortality data based upon death certificates, nevertheless, it is believed that the body of information being developed in this project will serve a number of useful

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

purposes in the search for etiological agents in the human population. For example, geographical patterns may evolve to suggest new leads for detailed field investigations and experiments designed to explain marked differences in observed lung cancer rates; the data are already serving in tests of previously announced impressions and hypotheses based on short-term observations; they will provide handy reference material as new leads are developed in experimental laboratories, and finally, they will be highly desirable as a baseline against which to compare future information.

e. Proposed Course of Project

1) This project should be finished during 1955. However, significant findings may be followed into later years, and it may be sesirable to purchase similar data for other cancer sites in other states.

2) No publications to date.

PROJECT REPORT FORM (Cont'd)

10. NCI-131
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 5,662	1	1	2	1/3	2/3	1	0
FY 1956	$ 6,338	1	1	2	1/3	2/3	1	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations & Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Oklahoma City, Oklahoma
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-132
SERIAL NO

6. Cancer experience in community population exposed to unusual radon gas concentration.
PROJECT TITLE

7. Pope A. Lawrence and Phillip Morgan
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

This is one of several related field study projects being conducted to determine possible association between occurrence of cancer in human population groups and long time exposure to elevated atmospheric concentration of naturally occurring radioactive substances.

b. Methods Employed

1) Environmental data with respect to atmospheric concentration of airborne radioactive substances in the study area have been collected by grab-type sampling flasks and assayed by the Occupational Health Program Field Station at Salt Lake City, Utah. Additional samples are to be taken and assayed on the spot using more recently developed field sampling and measurement method.

2) Biometrical evaluation is to be made of long time cancer mortality data being obtained from the National Office of Vital Statistics and the Arkansas State Vital Statistics Office. This information will be compared to cancer deaths expected if National or State average cancer death rates (corrected for age, etc) were to apply.

C. Major Findings

Data available permit of only tentative impressions:

1) The atmospheric concentration of radon in the study community may

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

well be several times the maximum permissible concentration presently recommended by the National Committee on Radiation Protection.

2) Examination of cancer mortality data tabulated for a ten year period established that reported respiratory cancer occurs at a higher rate in the study county (Garland) than in Arkansas as a whole. In the period 1939 to 1948 the average annual respiratory cancer mortality rate (age adjusted) for the county was twice that for the state.

d. Significance to Cancer Research

1) This study is providing data relative to the possible role of naturally occurring ionizing radiation and human cancer. If it yields sound impressions which can be duplicated from other localities, then an important step will have been taken toward one rational explanation of apparent geographical variation in occurrence of some cancers.

2) Knowledge accumulated with respect to possible effects of atmospheric concentration of radioactive substances in the community under study will be of value in future consideration of maximum permissible concentration of radioactive substances that may be released into the environment.

e. Proposed Course of Project

1) Continuing collection of atmospheric radioactivity data in the study community and county.

2) Continuing collation and biometric analysis of cancer mortality records for cancer of all sites for selected counties in Arkansas and for the State as a whole; through cooperation of the State Health Department and the National Office of Vital Statistics.

3) As appropriate, local environmental and population data and pertinent specific data on reported cancer deaths in the area will be gathered by staff personnel to whom this project is assigned.

PROJECT REPORT FORM (Cont'd)

10. NCI-132
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 2926	2	0	2	1/3	0	1/3	0
FY 1956	$ 3,152	2	0	2	1/3	0	1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Arkansas State Department of Health.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Boston, Mass.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-133
SERIAL NO

6. A Study of Lymphoma Cases Treated in a Selected Hospital in New England, Including Observations on Patients and Record.
PROJECT TITLE

7. Dr. John Vander.
PRINCIPAL INVESTIGATOR(S)

8. S. Ingraham
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

A survey of environmental and clinical factors common to patients with lymphoma.

(A) Objectives.
To obtain data relative to environmental, medical, personal, and family factors that may be associated to a greater degree than normal for patients developing lymphoma.

(B) Methods Employed.
Preliminary phases of the study will consist of two parts as follows: 1) Review of records for the past two years of patients admitted to the hospital with lymphoma, for the purpose of determining factors which may be commonly associated with this disease. 2) The study of patients currently being treated, with additional emphasis on environmental and occupational histories, to elicit factors that may have a common basis in this group. Patient material. All patients with lymphoma admitted to a large teaching hospital (approximately 450 beds, in a New England area).

(C) Major Findings.
Preliminary survey indicates that records are very complete, diagnostic facilities are excellent, and diagnoses almost invaribly are confirmed by tissue study. Except for these findings, there are no findings in regard to the study since it is just now developing.

(D) Significance to Cancer Research.
With the exception of x-radiation, and with the exception of vague reports on benzol exposure, environmental factors which are common to groups of patients afflicted with lymphoma are not known. Such data are of importance in any attempt

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION

(D) Significance to Cancer Research (Continued)
to elicit the etiologies of this disease, since it is recognized that any information on causitive factors have a marked practical effect in preventive measures which may be taken, since no curative therapy is available.

(E) Proposed Course of Project.
The study will be developed along plans outlined, and any specific leads developed will be followed-up. It is not possible at this moment to predict in what direction the major emphasis will be placed, since the study is in reality a broad investigation aimed at determining specific fields of endeavor that might be profitable for further study.

PROJECT REPORT FORM (Cont'd)

10. NCI-133
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 4,507	2 ~~1/2~~	0	2	1/2	0	1/2	0
FY 1956	$ 4,727	2 ~~1/2~~	0 ~~1~~	2 ~~1 1/2~~	1/2	0	1/2	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This project is very similar to the environmental studies being conducted at Children's Hospital by Dr. Manning on the parents of children who have developed leukemia.

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations & Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Boston, Mass.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-134
SERIAL NO

6. Cancer Incidence in a population of 5000 persons examined periodically.
PROJECT TITLE

7. J. Vander
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

1) To determine the incidence of cancer of major sites in a selected population under continuing and regular medical observation.

2) To inquire into possible etiologic factors of any unusual increase or decrease of cancer incidence (as compared to general population data) in the study population.

b. Methods Employed

1) The population numbering about 5000 persons has been receiving biennial physical examinations with emphasis on detection of early signs of heart disease. The present project represents an intensification of emphasis on search for cancers that are accessible to direct examination. Such cancers are known to represent more than 50% of all cancers.

2) There is, of course, prompt follow-ups on individuals of the study group found at examination to have symptoms or signs of less accessible disease.

c. Major Findings

1) A group of approximately 100 solitary nodules of the thyroid gland have been discovered, of which 10% have been removed by surgery. The remainder will be kept under observation to determine subsequent changes.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

d. Significance to Cancer Research

1) Makes available more data on occurrence of cancer in a selected, well deliniated group of statistically workable size.

2) In particular will provide information about the frequency of malignancy in solitary nodules of the thyroid gland.

3) This well documented, forward-looking study is expected to furnish a needed test of the usefulness of occupational history data in predicting possible environmental influences on occurrence of cancer.

e. Proposed Course of Project

1) In line with previously established procedures, one-half of the population group will be examined annually.

2) Any cancer discovered will be treated and the patients will be marked down for particular follow-up.

PROJECT REPORT FORM (Cont'd)

10. [illegible]
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 2,926	1	0	1	1/3	0	1/3	0
FY 1956	$ 3,152	1	0	1	1/3	0	1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

National Heart Institute

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

5. NCI-134
SERIAL NO.

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5. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Significance of Solitary Nontoxic Thyroid Nodules
Vander, John B., Eugene A. Gaston + Thomas R. Dawber
New England Journal of Medicine 251: 970-973, December 1954

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7. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Providence, R.I.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-135
SERIAL NO

6. Frequency of Occurrence of Cancer and Other Major Diseases Among a Group Covered by a State-wide Unemployment Insurance.
PROJECT TITLE

7. Dr. J. Vander Dr H Dorn
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives.

The objective of this project is to determine the prevalence, and if possible to obtain incidence rates on the occurrence of cancer of the major sites among selected occupational groups.

(B) Methods employed.

In one State, unemployment insurance covers a population group ranging roughly from 236,000 to 300,000. Insurance is compulsory for all persons who ordinarily come under social security regulations; that would be most persons working in establishments employing four or more persons. Female workers make up 42 percent of this total, and account for much of the fluctuation in the total size of the group.

Monthly reports of all primary malignancies of the lung and respiratory tract have been collected by Dr. Vander since the month of July 1953. Since July 1953 all disabilities occurring in this population group have been coded by the "International Classification of Disease", in three digits. Cases reported to date include social security number, age, sex, morbidity code and a brief occupational history.

After review of the problem, it was decided that cancer of all sites and major diseases would be collected in this manner. It was estimated by Dr. Dorn that reasonable population figures would be estimated from the census of the State for the groups desired. In addition, on each case of lung cancer, an occupational history will be obtained by an interviewer from the Unemployment Compensation Commission Office, in conjunction with Dr. Vander.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION (Continued).

(C) Major findings.

It is anticipated that this project may obtain incidence rates for various occupational groups, for cancer and other major disease sites. Data to date is insufficient for conclusion to be drawn.

(D) Significance to cancer research.

With very few exceptions, no incidence rates for cancer or other diseases are available on localized occupational groups. Precise information on these points would have definite bearing on further study of the etiologies of those cancers believed to be or questionably considered to be of environmental origin. Further progress in the field of environmental cancer can only be obtained by the collection of such data as described above.

(E) Proposed course of project.

For the present, occupational histories will be obtained only upon lung cancer patients, but cancers of all sites with occupation listed, and other major disease sites, with occupation listed will be collected. Prevalence rates will be obtained by combining this information with the appropriate population groups. In addition, occupational histories may be extended beyond the lung cancer group, dependent upon the preliminary findings.

10. NCI-135
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$2,926	1 ~~1/3~~	0 ~~1/3~~	1 ~~2/3~~	1/3	0	1/3	0
FY 1956	$3,152	~~1/3~~ 1	~~1~~ 0	~~1 1/3~~ 1	1/3	0	1/3	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Office of Biometry of the National Institutes of Health.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This study is somewhat similar to the study of the uranium miners to determine the incidence of respiratory cancer in that group, as conducted by the Field Investigations and Demonstrations Branch, the Atomic Energy Commission, the Division of Occupational Health. It would complement the study on absenteeism done by the Division of Occupational Health. Apart from these, I believe there are no other similar studies, and there are none of this specific type.

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Oklahoma City, Okla.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-136
SERIAL NO

6. Cancer Incidence in Selected Population Groups in Alabama.
PROJECT TITLE

7. Dr. Philip Morgan, Dr H Dorn
PRINCIPAL INVESTIGATOR(S)

8. P. Lawrence
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objective.
To determine the frequency of occurrence of cancer of different sites among selected population groups.

(B) Methods Employed.
From a list at hand of over 750 employees of various units, which were collected in the year 1947, a study will be made from the States Vital Statistics Departments and other registries to determine the number of patients in this group who have expired, and the cause of death. In addition, the main occupation as noted on the death certificate will give sufficient information to classify the patient as belonging to one of the groups under study. In this manner the frequency of occurrence of cancer of major sites among the population groups in question will be sought.

(C) Major Findings.
This study is now in the process of starting. It gives potential promise of furnishing prevalence rates for the year 1947.

(D) Significance to Cancer Research.
Prevalence and incidence rates in selected occupational groups are available in only very rare instances. Further information upon the etiologies of environmental cancer depend upon the acquiring of such information.

(E) Proposed Course of Project.
During the coming year the number of deaths in each population group will be determined, together with the cause of death. These will be used as leads to suggest further environmental cancer studies in any selected portions of the group where the prevalence appears to be increased.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-136
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

10. ______
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 2,926	2 ~~1/3~~	—	2 ~~1/3~~	1/3	—	1/3	—
FY 1956	$ 4,727	2	-	2	1/2	-	1/2	-

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This resembles the project previously described, being conducted by Dr. Vander in Boston, and is similar to the current project being conducted on the Civil Service Commission's cases by the Central Investigating Unit.

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations & Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Oklahoma City, Oklahoma
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-137
SERIAL NO

6. Etiology of lung, laryngeal and bladder cancer in New Orleans, Louisiana.
PROJECT TITLE

7. P. Morgan; M. Erjavec
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objectives

1) To verify the existence of high occurrence rates of lung, laryngeal and bladder cancer apparent in New Orleans, La. from a study of the 1947 morbidity-mortality records.

2) To seek information relating to the cause of the high level of cancer occurrence in the New Orleans area.

3) To develop and test practical methods of collecting supplementary data in areas previously surveyed in order to evaluate possible reasons for unusually high or low incidence of cancer.

b. Methods Employed

1) Reported morbidity and mortality information was collected and analyzed biometrically.

2) Over-reporting was minimized by reinvestigating residence status of cases through death certificate inspection, hospital record review, use of city directories and telephone directories and by personal interview of patients, relatives or friends.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-137
SERIAL NO.

3) Review of category assignment of diagnoses by checking original survey records for possible errors in coding, by examination of hospital clinical records for discrepancies between final diagnoses on the hospital records and the survey records and by inspecting death certificates for reported diagnoses.

4) To seek information pertinent to the cause of the high cancer occurrence rate in the New Orleans area special attention was directed in a selected study group, to additional collection of detailed family medical histories, occupational histories, unusual environmental circumstances, geographical distribution of cancer cases within the city limits of New Orleans, and possible presence of air pollutants or smog.

c. Major Findings

1) The increased occurrence rates of cancer of the lung, larynx and bladder in New Orleans cannot be explained away as an artifact on the basis of: (a) non-residency of any great proportion of the cases. (b) errors in coding or reporting of the cases.

2) Even when the New Orleans figures are corrected for non-residency and coding errors, the lung, larynx and bladder cancer rates remain higher than those of 9 other cities whose records were examined. It should be noted that New Orleans retains first place even though the data for the other areas was not corrected for errors of residency and coding.

3) No leads were discovered in the small group of families interviewed personally for occupational and environmental histories.

4) There was no observable geographical grouping of cases within the New Orleans area.

5) For guidance in future similar studies the following information was gained:

(a) Prior to coding and analysis, the original survey cards should be reviewed carefully to determine which cases have diagnoses established beyond question and which cases should be reviewed carefully prior to their inclusion in the study. (i.e. DIAGNOSIS SHOULD BE CONFIRMED BEFORE BIOMETRIC ANALYSIS OF THE DATA)

(b) Local medical societies and practicing physicians should have the project explained fully so their cooperation may be solicited directly and their reservation regarding the procedures discovered promptly.

(c) Time lapse between an original survey and the follow-up study should not be so long that hospital and other records are difficult to obtain access to and that cases and/or relatives may be difficult to trace.

(d) Unless a person has followed a single occupation throughout his lifetime the family and the hospital records usually cannot reveal his occupational history with any degree of accuracy.

d. Significance to Cancer Research

This project is a logical follow-up procedure on field researchers in cancer already accomplished. Through it the fact of increased cancer occurrence

of certain sites in the New Orleans area has been confirmed.

Negative evidence for selected possible reasons for the increased rates has been gained and procedural information that will be most useful in future cancer field studies has been gained.

e. Proposed Course of the Project

On-the-spot activities in the New Orleans area have been completed for the present. The data obtained is being collated and considered. A report for possible publication is being prepared.

Similar investigation of other of the 10 cities in the Ten City Cancer Morbidity-Mortality Survey is being contemplated as funds and personnel allow.

Environmental and air pollution data in New Orleans are being collected by other activities of the Public Health Service. When reports on the findings of these activities become available, these data will be collated with our cancer study data in search of possible causes for the observed elevation cancer occurrence in New Orleans.

PROJECT REPORT FORM (Cont'd)

10. NCI-137
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 2,926	2	-	2	1/3	-	1/3	-
FY 1956	$ 3,152	1	-	1	1/3	-	1/3	-

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

New Orleans Medical Society

Charity Hospital, New Orleans, La

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE

NO ENTRIES FOR 15, 16 & 17.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Field Investigations and Demonstrations Branch
LABORATORY OR BRANCH

3. Field Studies Section
SECTION OR SERVICE

4. Oklahoma City, Oklahoma
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-138
SERIAL NO

6. Study of Occupational Histories of a selected group of patients with cancer of the skin.
PROJECT TITLE

7. P. Morgan
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. Objective

1) Identification of environmental or occupational factors in a selected State that may be causes or contributory factors in the occurrence of cancer of the skin.

2) Study of selected skin cancer patients for predisposing factors in occurrence, recurrence or repeated occurrence of cancer of the skin.

b. Methods Employed

1) Occupational and pertinent environmental history information is being gathered on several selected hospital case groups diagnosed as having skin cancer.

2) The study group, as practicable, will be enlarged by inclusion of data on patients of practicing physicians who cooperate in the project.

3) Individual cases will be followed for a number of years to learn about recurrences or occurrence of additional skin cancers.

4) The compiled study data will be examined for indication of occupational or geographic factors common to groups of cases that might emerge as possible etiologic factors in skin cancer.

c. Major Findings

1) None. This project is just starting.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION (continued)

d. Significance to Cancer Research

1) Exposure to sun and the elements as well as exposure to petroleum products have long been suspect as causes of skin cancer in the general population. This study group will be comprised to a great extent of outdoor workers and of petroleum workers. It is expected that specific information will be evolved relative to the rate of exposure and of crude petroleum products in production of skin cancer.

e. Proposed Course of Project

1) All skin cancer patients treated at two major hospital dispensaries plus patients referred by cooperating practicing physicians will be interviewed for special environmental and occupational histories.

2) Patients will be followed through clinic resources and by personal contact. Periodically, contact will be made with State and local vital records services to pick up death certificate information on patients who may have succumbed.

3) As data accumulates it will be collated and analyzed biometrically in search for possible etiologic factors of skin cancer.

PROJECT REPORT FORM (Cont'd)

10. NCI-138
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$2926	1	0	1	1/3	0	1/3	0
FY 1956	$4,727	1	0	1	1/2	0	1/2	0

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR 15, 16 & 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry & Epidemiology Branch
LABORATORY OR BRANCH

3. Office of Chief
SECTION OR SERVICE

4. ----
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-050
SERIAL NO

6. Statistical studies on patients with neoplastic diseases
PROJECT TITLE

7. Michael B. Shimkin
PRINCIPAL INVESTIGATOR(S)

8. K. C. Oppermann, B. V. A. Low-Beer, W. L. Bostick
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Project: Statistical studies on patients with neoplastic diseases.

Objectives: To analyze the distribution and survival of patients with specific neoplastic diseases.

Methods: Examination of hospital records, follow-up and analysis of patients recorded at the University of California Hospital, 1913 to 1951.

Major findings: During 1954, analysis was carried out on 254 patients with Hodgkin's disease.

The duration of illness from Hodgkin's disease, as determined from apparent onset to death, showed no significant changes during the period 1913 to 1951. The mean survival was 44.3 months; the five-year survival was 26.5 percent. The five-year survival from date of diagnosis was 18.6 percent.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-050
Serial No.

PROJECT REPORT FORM (Cont'd)

There was significantly longer survival in females than in males. At five years after onset, 36.6 percent of 93 females and 20.9 percent of 161 males were alive. The ancillary use of estrogens in the management of Hodgkin's disease in males was suggested.

There was no significant correlation between survival and age at onset. No statistically significant effects could be correlated with various major forms of treatment. Nitrogen mustard, used in 65 patients, produced no demonstrable prolongation of life.

Significance to cancer research: Provides essential baselines for comparisons of effects of newer methods of treatment, as well as records changes in distribution and duration of disease during a thirty-five year span.

Proposed course: Transfer and expansion of the studies from California to Bethesda. Use will be made of patients with cancer recorded during the 1947-48 ten-city survey to determine survival during subsequent five-year period. A methodical analysis will be made of sex and age distributions in the lymphomas recorded in the national mortality statistics, 1920-1950.

PROJECT REPORT FORM (Cont'd)

10. NGI-050
SERIAL NO.

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11. **BUDGET DATA:**

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7295 5,000	1/2	--	1/2	1/2	1/2	1	
FY 1956	$14,593 ~~5,000~~	1	1	2	1	1	2	

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12. **BUDGET ACTIVITY:**

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Unknown; probably none.

5. NCI-050
SERIAL NO.

6. **PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:**

(1) Shimkin, M. B., Oppermann, K. C., Low-Beer, B. V. A., and Mettier, S. R.: Lymphosarcoma. An analysis of frequency, distribution and mortality at the University of California Hospital, 1913-1948. Ann. Int. Med., 40: 1095-1107, 1954.

(2) Shimkin, M. B., Lucia, E. L., Low-Beer, B. V. A., and Bell, H. G.: Recurrent cancer of the breast. Analysis of frequency, distribution, and mortality at the University of California Hospital, 1918 to 1947, inclusive. Cancer 7: 29-46, 1954.

(3) Shimkin, M. B., Oppermann, K. C., Bostick, W. L., and Low-Beer, B. V. A.: Hodgkin's disease. An anlysis of frequency, distribution and mortality at the University of California Hospital, 1914-1951. Ann. Int. Med., 41: Dec. 1954.

(4) Shimkin, M. B.: Chemotherapeutic management of lymphomas; effect upon survival. Acta Unio Contra Cancrum (in press). Delivered on panel on leukemia at Sixth International Cancer Congress, Brazil, August 1954.

(5) Shimkin, M. B., and Field, J. B.: Chemotherapy of Cancer. In: Fundamentals of Cancer Practice. (To be published 1955).

7. **HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:**

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry & Epidemiology Branch
LABORATORY OR BRANCH

3. Office of Chief
SECTION OR SERVICE

4. ----
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-051 ----
SERIAL NO.

6. Quantitative studies on pulmonary tumors in mice.
PROJECT TITLE

7. Michael B. Shimkin
PRINCIPAL INVESTIGATOR(S)

8. Milton J. Polissar
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Project: Quantitative studies on pulmonary tumors in mice.

Objectives: To contribute to knowledge regarding induction and growth of tumors, using the pulmonary tumor of the mouse as the biologic system.

Methods: Quantitative measurement of cell numbers, size of hyperplastic foci and of tumors in lungs of mice at regular intervals following urethan. Mathematical analysis of the findings.

Major findings: Analysis of surface tumors revealed that (a) the occurrence of such tumors belongs to the class of rare events and is subject to Poisson's distribution, and (b) deviation from Poisson's distribution may be interpreted in terms of the heterogeneity of the susceptibility of the animal population.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM

Detailed study of strain A mouse lungs following a single dose of 1 mg. urethan per gram body weight showed that within a day there began an increase in the cellular number, which doubled the number of cells by four weeks. At three weeks circumscribable hyperplastic foci appeared; by 5 weeks there were 600 such foci per lung. Earliest pulmonary tumors were recognized at 3 weeks; the number increased to 36 per lung by 7 weeks and then remained at that level. The mean doubling time of tumors is 4.4 days up to 7 weeks and then the rate of growth decreases, so that between 12 and 19 weeks the mean doubling time is 55.5 days. At 19 weeks, the pulmonary tumors occupy only 1 percent of the lung volume and represent 2.5 percent of the cell population of the lung.

Significance to cancer research: The quantitative histologic approach to this material allows more detailed observations on earlier phases of the initiation and growth of one typical animal neoplasm.

Proposed course: If laboratory space becomes available, it is hoped to extend the observations to induction of tumors in less susceptible strains, such as C_3H and with a few widely separated doses of urethan, in order to clarify the relationships of hyperplasia and neoplasia in this biologic system.

PROJECT REPORT FORM (Cont'd)

10. NCI-051
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7,295 ~~1,000~~	1/2	-	1/2	1/2	1/2	1	
FY 1956	$7,297 ~~1,000~~.	1/2	-	1/2	1/2	1/2	1	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

4, IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Unknown; probably none

PROJECT REPORT FORM (Cont'd)

15. NCI-051
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

(1) Shimkin, M. B.; Pulmonary tumor induction in mice with chemical agents used in the clinical management of lymphomas. Cancer, 7: 410-413, 1954.

(2) Polissar, M. J., and Shimkin, M. B.: A quantitative interpretation of the distribution of induced pulmonary tumors in mice. J. Nat. Cancer Inst. 15: 377-403, 1954.

(3) Shimkin, M. B.: Pulmonary tumors in experimental animals. Advances Cancer Research, 3: (In press).

(4) Shimkin, M. B., and Polissar, M. J.: Some quantitative observations on the induction and growth of primary pulmonary tumors in strain A mice receiving urethan. J. Nat. Cancer Inst. (In press).

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Biometry and Epidemiology Br.
LABORATORY OR BRANCH

3. Epidemiology
SECTION OR SERVICE

4. Pittsburgh, Pa.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-052
SERIAL NO

6. Epidemiology of Cancer of the Lung, Pittsburgh Field Study
PROJECT TITLE

7. Sr. Asst. Surg. C. D. McClure
PRINCIPAL INVESTIGATOR(S)

8. Dr. W. McD. Hammon and Dr. A. Ciocco, Graduate School of Pub. Hlth.,Univ. of Pitt.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: (a) To investigate the clinical and environmental circumstances under which representative cases of cancer of the lung occur in a general population and to determine the characteristics which distinguish people who develop the disease from those who escape it. (b) To evaluate the mass small film X-ray survey as a case finding tool.

Methods Employed: (a) Personal interview of all cases diagnosed over a period of several years, together with collection of similar data from a control population. (b) Follow-up, through death certificate data of survey and non-survey population; and special and detailed follow-up of selected sample of X-ray examinees who had certain lesions, together with a control group who were negative to X-ray.

Major Findings: None in the general study, field work on which is just commencing.

About the same proportion of tumor suspects and cases of lung cancer were found in the Pittsburgh Survey as previously found in others. However, no detailed results in evaluation contemplated in this study may be expected for several years.

Significance To Cancer Research: Provides basic information regarding pathogenesis and epidemiology of cancer of lung which cannot be determined any other way.

Proposed Course of the Project: Continued follow-up of the study subjects to death or over a period of several years - at least until lung cancer rates in Survey and Non-Survey population are equal.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-052
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$22,490	1	3	4	1	2-1/2	3-1/2	
FY 1956	$39,822	2	4	6	2	4	6	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

This study operates parallel to other field studies of cancer conducted by the Biometry Section, NCI. Both field and NCI Headquarters staff of the 2 sections collaborate in planning and operation of the 2 studies.

4, IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-062
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

McClure, C. D. Bull. Allegheny Co. Med. Soc. In Press.
The "Negative" Chest Film. A Case Report from the "Coin" Lesion Follow-up Study of the 1953 Pittsburgh and Allegheny County Mass Chest X-ray Surgery.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Dr. McClure has been appointed Research Assistant in the Department of Epidemiology, University of Pittsburgh Graduate School of Public Health and has been accepted as candidate for the Doctorate in Public Health.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Biometry and Epidemiology Br.
LABORATORY OR BRANCH

3. Epidemiology
SECTION OR SERVICE

4. New York City
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-053
SERIAL NO

6. Cancer in a closed population
PROJECT TITLE

7. Medical Director Alexander G. Gilliam
PRINCIPAL INVESTIGATOR(S)

8. Sidney J. Cutler (Biometry Section)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Primary objective is to measure risk of death from all causes, but particularly from cancer of the lung, in a closed employee population some of whom are excessively exposed to gasoline and disel engine exhaust fumes.

Methods Employed: Analysis of work records of about 60,000 men employed between 1906 and 1953; determining cause of death in those dead; and comparing death rates in this population with that for other men in the same city.

Major Findings: Study will not be completed prior to FY 1956 or FY 1957.

Significance to Cancer Research: To provide a partial test to the idea that gasoline and diesel engine exhausts are carcinogenic to the human lung. Will also provide material for studies in methodological problems involved in analyzing occupational data as related to disease.

Proposed Course of Project: Complete tracing cause of death which is now about 90% complete; code the employment and death data; compute expected and observed death rates; and make appropriate comparisons.

PROJECT REPORT FORM (Cont'd)

10. NCI-053
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$13,640	1	2	3	1/3	2	2-1/3	
FY 1956	$13,728	2	2	4	1/3	2	2-1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Biometry Section, NCI. Some coding will be contracted for with National Office of Vital Statistics. Other coding and tabulating will be performed by Tabulating Unit, NIH.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Biometry and Epidemiology Br.
LABORATORY OR BRANCH

3. Epidemiology
SECTION OR SERVICE

4. Buffalo, New York
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-054
SERIAL NO

6. Epidemiology of Leukemia and the Lymphomas
PROJECT TITLE

7. Sr. Asst. Surg. Donald MacDonald
PRINCIPAL INVESTIGATOR(S)

8. Dr. Wendell Ames, Erie County Health Department
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Objectives: To determine the clinical and environmental circumstances surrounding the development of leukemia in a general population and to determine the characteristics of persons who do and do not develop the disease.

Methods Employed: By interview to obtain comprehensive epidemiological information about patients to compare with similar data obtained from controls, advantage being taken of the fact the disease is reportable in this area. Systematic clinical data also obtained from patients and from various clinical facilities.

Major Findings: Due to resignation of principal investigator project was not completed. Because of meager data available in 1 year, findings when analyzed, will probably be of value only from the standpoint of methodology.

Significance to Cancer Research: If completed as planned, would have provided basic epidemiologic information regarding leukemia and the lymphomas as they occur in a general population as opposed to data now available only from highly selected hospital experience.

Proposed Course of Project: If suitable officer can be obtained, project will be reinstituted.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-054
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$16,620	2	1	3	1-1/2	1/2	2	
FY 1956	$11,934	1	1	2	1	1/2	1-1/2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-054
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Meadors, G. F. Epidemiology of Leukemia. Pub. Hlth. Rpt. In press.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Dr. Gilcin F. Meadors
Appointed to Medical Advisory Board, National Blood Foundation.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Epidemiology
SECTION OR SERVICE

4. Bethesda, Md.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-055
SERIAL NO.

6. Studies in Geographic and Racial Distribution of Cancer
PROJECT TITLE

7. Sr. Surg. Robert Lincoln Smith , Medical Director Benno K. Milmore
PRINCIPAL INVESTIGATOR(S)

8. Dr. Clarence Salsbury, State Health Officer, Phoenix, Arizona
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Objectives: General - To determine racial and geographic factors influencing risk to cancer.

Specific: (a) Study of cancer among the Navajos. (b) Geographic distribution of cancer of the lung in the United States. (c) Trends of mortality from cancer of the lung in the United States. (d) Study of mortality from cancer in minor non-white races in the United States and Hawaii.

Methods Employed: (a) A survey of all hospitalized illnesses and all recorded deaths among Navajos for a 5-year period. This disease and mortality experience will be compared with that of other Americans in an attempt to evaluate the apparent deficit of some forms of cancer among Navajos. (b, c, and d) Analysis of death certificate data obtained from official Vital Statistics records.

Major Findings: (a) Dr. Salsbury's impression of a deficit of recorded cancer of the breast in Navajos is substantiated but considerable further analysis of corollary data is necessary before its validity can be established.

(b) Marked variation among the States is noted in mortality attributed to cancer of the lung. This extends to the large cities of 100,000 or more population where a 5-fold difference exists between the cities with highest and lowest rates. The data provide no reasons for the great variation observed.

(c) A critical analysis of trends of mortality from lung cancer, [illegible], reveals that because of changes in nomenclature and Death Registration Area

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION - Cont'd.

no exact measure of trend is available for this period. The observed trend, however, is more marked among males than females, and more among non-white than among the white.

(d) Study incomplete but confirms the view that Japanese males are more at risk to gastric cancer, and Japanese females less at risk to breast cancer than their American counterparts.

Significance To Cancer Research: The epidemiological method depends for its success on the demonstration of differences in risk in people with different characteristics, environments, etc. Thus, the results of this project are descriptive and provide information for use in tests of consistency with a variety of theories of cancer causation, as well as leads for further exploration.

Proposed Course of Project: To be continued and expanded in similar direction with other cancers as suitable personnel become available.

PROJECT REPORT FORM (Cont'd)

10. NCI-055
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$23,441	2	2	4	1-2/3	1-1/2	3-1/6	
FY 1956	$21,890	2	2	4	1-1/2	1-1/2	3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Research of parallel character conducted by Biometry Section and Geographic Pathology Section.

15. NCI-055
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Hoffman, E. F. and Gilliam, A. G. Lung cancer mortality. Geographic distribution in the United States for 1948-49. Pub. Hlth. Rpt. 69: 1033-1042 (Nov.) 1954.

Gilliam, A. G. Mortality attributed to cancer of the lung in the large cities of the United States, 1948-49. J. Nat. Cancer Inst. In press.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Biometry and Epidemiology Br.
LABORATORY OR BRANCH

3. Epidemiology
SECTION OR SERVICE

4. Bethesda, Md.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-066
SERIAL NO

6. Research in epidemiological method
PROJECT TITLE

7. Medical Director B. K. Milmore, Medical Director A. G. Gilliam
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Objectives: To examine recorded epidemiological evidence in cancer for its validity and to develop more adequate epidemiological tools for cancer investigation.

Methods Employed: Adaptation and modification of standard epidemiological methods already of demonstrated usefulness in communicable diseases research, and extension and application of these methods to cancer study; including the application of such methods to published data for test of validity of conclusions drawn.

Major Findings: It has been shown that published data bearing on increased risk to cancer of the liver in the Bantu have been exaggerated and more adequately reflect an extraordinary deficit of cancer of other sites.

Some progress is being made in development of an adequate method of handling case history data relating to occupational risk to cancer. An attempt is being made to apply this method to a series of cases of cancer of the lung.

An analysis of the epidemiological evidence bearing on the hypothesis that cigarette smoking is the major cause of lung cancer has led to the conclusion that though many of these facts are consistent with the hypothesis, some are inconsistent and the majority remain inadequately tested. The earlier conclusion of this Section therefore remains unchanged namely, that the etiological significance of the association between smoking and lung cancer is unestablished.

Significance to Cancer Research: Any theories of causes of cancer in humans, from no matter what scientific discipline they come, will remain inadequate until they meet the test of consistency with epidemiological facts. Hence, development of more precise and powerful epidemiological tools if of considerable importance to cancer research.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

9. PROJECT DESCRIPTION - Cont'd.

Proposed Course of Project: To be exploited as new ideas and opportunities arise.

10. NCI-056
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$14,116	2	2	4	2/3	1-1/2	2-1/6	
FY 1956	$14,160	2	2	4	2/3	1-1/2	2-1/6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Informal or formal statistical assistance from Biometric Section staff.

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-056
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Gilliam, A. G. A note on evidence relating to the incidence of primary cancer of the lung in the Bantu. J.N.C.I. 15: 195-199 (Aug.) 1954.

Gilliam, A. G. Some aspects of the lung cancer problem. Military Medicine. In press.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Biometry and Epidemiology Br.
LABORATORY OR BRANCH

3. Epidemiology
SECTION OR SERVICE

4. Bethesda, Md.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-057
SERIAL NO.

6. Stimulation of Epidemiological Research by Non-Service Agencies.
PROJECT TITLE

7. Medical Director Alexander G. Gilliam
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To stimulate the inauguration of epidemiological studies of cancer among people and agencies who have material, the exploitation of which will contribute to an understanding of human cancer; and to provide assistance in its analysis.

Methods Employed: Through meetings of national associations, lectures before medical and public health students and exploitation of personal friendship with persons in many agencies, to encourage and help plan studies of their own material.

Major Findings: A study of cancer among a large free living population in which there are social restrictions against use of alcohol, tobacco and coffee was stimulated and designed. Results have thus far been witheld.

Assistance in analysis of data provided to the medical director of a large industrial corporation designed to measure occupational cancer risks.

Assistance in analysis of cancer data, preparation of report and extension of studies provided a State Health Department director of industrial hygiene.

Conducted seminars at Pittsburgh and Johns Hopkins Public Health Schools; at the Army Medical Services Graduate School and Naval Medical School; and lectured to medical students at Syracuse and Rochester.

Significance to Cancer Research: The future of research in this field depends partly on exploitation of material not available to us and recruitment of future workers.

Proposed Course: Continue as opportunities arise.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCI-057
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 3,108	1	0	1	1/3	0	1/3	
FY 1956	$ 3,092	1	0	1	1/3	0	1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Biometry Section provides consultative services.

15. NCI-057
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Gilliam, A. G. Epidemiological method in non-communicable diseases. Pub. Hlth. Rpt. 69: 907-913 (Oct.) 1954.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-05 8
SERIAL NO

6. Vaginal Cytology Survey, Memphis, Tenn.
PROJECT TITLE

7. Dr. Baum, Dr. Erickson (Univ. of Tenn.)Mr. Cutler, Mr. Greenhouse (NIMH)
PRINCIPAL INVESTIGATOR(S)

8. NONE
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives: ~~Provide bas~~ic data on cancer incidence, prevalence, and mortality in the United States. Investigate effect of various epidemiologic faftors such as color, sex, age, geographic region, and economic status.

(B) Methods Employed: Approximately 85,000 women have been examined once. The second round of examinations is now under way. A third round is planned. Some 25,000-35,000 women are expected to be screened three times.

Ahother morbidity survey will be carried out upon completion of the screening program (1957), so that the effects of the program on the incidence of cervical cancer may be evaluated.

(C) Major Findings: Of the first 70,000 women screened, 1,327 had positive or suspicious smears. Biopsies were completed on 1,076 (81%) of the 1,327. The biopsy findings were positive on half the group and suspicious on an additional 12 percent. Of the 282 cases of carcinoma-in-situ diagnosed, 88 percent were previously unsuspected; of the 245 cases of cervical cancer, 29 percent were unsuspected. Of the carcinoma-in-situ group 68 percent were under 40 years of age, compared with 18 percent of the invasive carcinoma group.

(D) Significance to cancer research: Provides basic epidemiologic information regarding the incidence of cancer.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. VC1-058
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$1,166	1 4/8	—	1 4/8	1/8	—	1/8	
FY 1956	$ 6,477	1 4/8	1	2 4/8	1/8	1	1 1/8	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

University of Tennessee is providing top level professional supervision. Memphis and Shelby County Health Department is providing nurses for follow-up on cases.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry & Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-059
SERIAL NO

6. Incidence of Lung Cancer Among World War I Veterans: Smokers & Non-Smokers
PROJECT TITLE

7. Dr. Baum and Dr. Dorn
PRINCIPAL INVESTIGATOR(S)

8. NONE
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION:** Major responsibility for this study rests with the Office of Biometry, NIH and the Field Studies Section, NCI. The Biometry Section is contributing supporting personnel services.

(A) Objectives: To determine by direct observation of a defined cohort the mortality from lung cancer among male smokers and nonsmokers.

(B) Methods Employed: The Veterans Administration will send a smoking questionnaire to all (about 300,000) World War I veterans covered in their insurance program. The veterans returning questionnaires will be classified according to smoking history and followed for a period of time (probably 5 years). The Veterans Administration routinely receives death benefit claims and arrangements have been made to copy and transmit this information to the investigators which can then be collated with the smoking histories.

(C) Major Findings: Study will begin in last half of current fiscal year; no findings to date.

(D) Significance to cancer research: All published data on differential incidence and mortality from lung cancer among smokers and nonsmokers are based on indirect calculations drawn from the collection of smoking histories among lung cancer patients and controls. Biases can creep into studies of this nature, and the magnitude of the ratio of rates for smokers to nonsmokers range in different studies from two (2) to 14 times.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-059
Serial No.

PROJECT REPORT FORM(Cont'd)

Observation of defined cohorts over a period of time on a prospective basis will permit direct calculation of more reliable rates. It may later prove feasible to collect additional information on subsamples of the cohorts to test association with other factors.

PROJECT REPORT FORM (Cont'd)

10. NCI-059
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$9,065	1 1/8	2 1/2	3 5/8	1/8	1 1/2	1 5/8	
FY 1956	$ 6,477	1 1/8	1 1/2	2 5/8	1/8	1	1 1/8	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

NONE

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute

2. Biometry and Epidemiology Branch

3. Biometry Section

4. LOCATION (IF OTHER THAN BETHESDA)

5. NCI-060 SERIAL NO.

6. Survival Data on Cancer Patients Enumerated in Morbidity Surveys
PROJECT TITLE

7. William Haenszel
PRINCIPAL INVESTIGATOR(S)

8. NONE
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(A) Objectives: To extend survival information to cover a five year period for newly diagnosed patients enumerated in morbidity surveys. These data will be collated with the experience of cancer registers and of clinical series reported in the literature. The scope of the experience (45,000 cases) will permit systematic examination of such factors as color, sex, age, geographic region, place of treatment, and economic status, in addition to primary site.

(B) Methods Employed: Lists of cancer patients are being searched against death indexes maintained in vital statistics offices. In selected areas hospitals and physicians will also be contacted for further information on patient status and to estimate the loss to follow-up by reliance on vital statistics records only.

(C) Major Findings: No findings will be available until the end of the collection period, approximately 18-24 months.

PROJECT REPORT FORM

(D) Significance to Cancer Research: Survival experience of cancer patients is not very well documented. Most series are based on a limited number of cases and worse still, have not been analyzed in a uniform manner and have not included all cases coming into the field of observation. These survival data, when analyzed by standard definitions and methods will provide useful reference bench marks.

(E) Proposed course of this project for the succeeding calendar year: A monograph (or a series of reports dealing with individual sites) will be prepared analyzing the data and relating the findings to other published experience.

10. NCI-060
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$6,432	1	2	3	1/8	1	1 1/8	
FY 1956	$14,113	2	2	4	3/8	2	2 3/8	

12. BUDGET ACTIVITY:

RESEARCH [✓ X] ADMINISTRATION ___

REVIEW & APPROVAL ___ TECHNICAL ASSISTANCE ___

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956

None

No entries for 14, 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-061
SERIAL NO.

6. Consultation to Health Departments and Hospitals on Cancer Registers
PROJECT TITLE

7. William Haenszel
PRINCIPAL INVESTIGATOR(S(

8. Sidney J. Cutler and Samuel C. Marcus
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(A) Objectives: To assist state and local Health Departments and hospitals by giving consultation and advice on methodological problems in the maintenance of registers and on the analysis of data collected.

(B) Methods Employed: While many of the problems can be handled by correspondence, field trips are required in several instances. Consideration must be given to the objectives of the state and local programs, the existing administrative arrangements, and the personnel and financial means available to implement the program.

(C) Major Findings: In activities in 1954 the states receiving the largest amount of consultation were Connecticut, Florida, Kentucky and Vermont. In Connecticut the section cooperated in the draft of a report analyzing the first seventeen years' experience of the cancer register. A cancer control grant has been secured for the publication of this report which will appear in 1955.

PROJECT REPORT FORM

(D) Significance to Cancer Research: Cancer registers soundly conducted are a basic source of epidemiological information. In supporting state and local activities in this field the potential study resources of NCI and related organizations are enlarged.

(E) Proposed course of this project for the succeeding calendar year: The American College of Surgeons new program for tumor clinic accreditation, requiring maintenance of cancer registers, will foster the continued development of registers on a local and state level. An expanding volume of consultation work may be anticipated.

10. NCI-061
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,680	3	-	3	1/2	-	1/2	
FY 1956	$4,638	3	-	3	1/2	-	1/2	

12. ______
BUDGET ACTIVITY

RESEARCH X
ADMINISTRATION ___
REVIEW & APPROVAL ___
TECHNICAL ASSISTANCE ___

PROJECT REPORT FORM

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956.

Some of the computation work is done on request by the Field Investigations and Demonstrations Branch, which supplies data on Health Department organization and program activity.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH

15. NCI-061
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954

None

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-062
SERIAL NO.

6. Development and Application of Statistical Methods to Study of Cancer in Human Populations
PROJECT TITLE

7. William Haenszel
PRINCIPAL INVESTIGATOR(S)

8. All professional personnel on Section Staff
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(A) Objectives: To develop more powerful tools for field investigations of cancer and to stimulate wider application of the methods.

(B) Methods Employed: There are two general approaches. One consists of use of clinical and epidemiological records already available, for the contribution they can make to the study of understanding the distribution of cancer in human populations. Some attention has been given periodically to proper methods of analysis of occupation experience obtained from these sources. In the past year, special attention has been given to incorporating the findings of retrospective studies on smoking and lung cancer in cohort analyses of the probable future course of mortality from this disease.

In field research, methodological problems in retrospective case history studies and in prospective studies on defined population groups are being followed. For example, to disentangle the effects of age and duration of smoking as associated with lung cancer, a

retrospective study of smoking and lung cancer among women appeared indicated. A study is in progress on a closed population, some of whom are believed to be excessively exposed to gasoline engine exhaust fumes. The study should determine whether these persons have an excess lung cancer risk and will contribute data on methods for classification of population with respect to duration and intensity of risk. Conventional demographic data for the classification of populations usually are not etiologically meaningful for the computation of incidence rates for various cancer sites. Other sources of information must be developed. Arrangements have been made for the Bureau of the Census to collect smoking histories for a sample closed section of the U. S. population as part of one of its Current Population Surveys. This approach may later prove useful for collecting data on population characteristics in investigation of other cancer sites.

(C) Significance to Cancer Research: These are the sort of problems confronting investigators dealing with the distribution of cancer in human populations, where the controlled observational methods of animal experimentation cannot be applied.

(D) Proposed course of this project: for the succeeding calendar year: As individual projects are completed, papers will be written.

10. NCI-062
SERIAL NO.

11.
BUDGET DATA

	ESTIMATED	BUDGETED POSITIONS			MAN YEARS			PATIENT
	EXPENDITURES	PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
FY 1955	$ 9,928	3	2	5	1/2	1	1 1/2	
FY 1956	$ 9,956	3	2	5	1/2	1	1 1/2	

PROJECT REPORT FORM

12.
BUDGET ACTIVITY

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956

None

14. The Epidemiology Section of this Branch conducts parallel research
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH

15. NCI-062
SERIAL NO.

16.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954

Cutler, S. J., and Loveland, D. B.: "The Risk of Developing Lung Cancer and Its Relationship to Smoking." Journal of the National Cancer Institute, Vol. 15, No. 1, August 1954.

17.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section

4.
LOCATION (IF OTHER THAN BETHESDA

5. NCI-063
SERIAL NO.

6. Study of Mortality and Disability Retirement Due to Cancer Among Railroad Workers
PROJECT TITLE

7. Dr. William Baum and William Haenszel
PRINCIPAL INVESTIGATOR(S)

8. Benjamin Carroll
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: The study is being undertaken in cooperation with the Field Studies Section, Field Investigations and Demonstrations Branch

(A) Objectives: To determine occupational and other group differentials in the incidence of lung cancer (and other cancer sites) among railroad workers, which can then be used as leads for further detailed investigations (in cooperation with railroad medical departments) to test hypotheses on specific etiological factors.

(B) Methods Employed: A cohort of all working and retired railroad employees with at least ten years' exposure in the industry as of January 1, 1953 will be set up (approximately 1,000,000 persons). From its records the Railroad Retirement Board can assemble the population base data and information on mortality and disability retirement due to cancer for this cohort. A procedure has been worked out to assemble the information from the various sources and reproduce it on a special set of study punch cards, which can be placed at the disposal of the investigators. Sufficient identifying detail has been provided to make possible further studies of groups exhibiting unusually high rates. The Railroad Retirement Board under contract has supplied punch cards for the cohort under-study and is now searching their records and preparing reports on

PROJECT REPORT FORM

mortality and disability retirement for the first study year.

(C) Major Findings: The collection process continues and there are no findings to report as yet.

(D) Significance to Cancer Research: Railroad employees are an occupationally stable group, with their own retirement system. This is an ideal setting in which to attempt investigation of occupational factors and will provide good experience for later handling occupational data collected in Social Security Board operations. Certain railroad employees are known to be exposed to carcinogenic agents and we have here a direct means of observing the effects. With a defined cohort, holding certain occupational factors constant, it would be possible to supplement the RRB records with collection of additional details on personal histories (in cooperation with railroads) to test association with other factors.

(E) Proposed course of this project for the succeeding calendar year: At least two years mortality experience need to be collected before findings on occupational differentials and mortality can be reported. It is anticipated that mortality and disability retirement experience may be collected over a period of years and that details on specific occupations and exposures to suspected carcinogenic agents may be studied.

10. NCI-063
SERIAL NO.

11.
BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 1,166	2	0	2	1/8	0	1/8	
FY 1956	$ 2,318	2	0	2	1/4	0	1/4	

PROJECT REPORT FORM

12. BUDGET ACTIVITY

RESEARCH	X	ADMINISTRATION	___
REVIEW & APPROVAL	___	TECHNICAL ASSISTANCE	___

13. NONE

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

This study is being undertaken in cooperation with the Field Studies Section and Field Investigations and Demonstrations Branch

14. NONE

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

15. Ncl-063

SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954

None

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section

4.
LOCATION (IF OTHER THAN BETHESDA

5. NCI-064
SERIAL NO.

6. Investigations in the Geographical Pathology of Uterine Cancer
PROJECT TITLE

7. Dr. Harold L. Stewart and Dr. Harold F. Dorn
PRINCIPAL INVESTIGATOR(S)

8. Donald B. Loveland
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(A) Objectives: Striking differences reported in various geographical areas or racial stocks in the frequencies of cancers of different anatomical sites are under investigation as they may aid in determining factors in the etiology of certain cancers. Currently a study of uterine cancer (uterine cervix and corpus) in Jewish, non-Jewish white, and negro patients is being conducted to facilitate further understanding of the different incidences noted in these groups.

(B) Methods Employed: The study is being pursued by a group of trained investigators, in New York City and Israel. Coding of the results and a statistical analysis will be made at the National Cancer Institute. Reported incidences of cervical cancer are greatest in Negro, least in Jewish women.

Three parallel aspects of the study are being pursued:

1. Obtaining records of all uterine cancer cases diagnosed during the period of study in the areas indicated, with

PROJECT REPORT FORM

information on the patient's color, religion, age, exact diagnosis, etc. (In Israel, breast cancer and other female genital cancer are also being investigated.)

2. Interviewing of all uterine cancer patients possible, and an equal number of control patients with a view to establishing any factors in the patient's past history worthy of further study in elucidating differences in uterine cancer incidence.

3. Pathologic Study of material from all possible cancer cases in the above study.

(C) Major Findings: Preliminary findings to date indicate that there are about 4.5 cases of cancer of the corpus to 1 case of cancer of the cervix in the Jewish women in Israel. In New York City the corresponding ratio among Jewish women is approximately 3 to 1. In the non-Jewish white female population of New York City, this ratio is reversed; the ratio of cases of cancer of the cervix to cases of cancer of the corpus is approximately 2 to 1. Preliminary data from other sources indicate a ratio of cases of cancer of the cervix to cancer of the corpus of approximately 15 to 1 among negro females.

(D) Significance to Cancer Research: See 9A.

(E) Proposed course of this project for the succeeding calendar year: The collection of histories in New York City and Israel is now virtually complete. The pathologic review of study material is also nearing completion. Final coding of the records awaits the completion of the pathologic review. The analysis of the New York City incidence data will be completed in 1955 and detailed analysis of the data for case and control series will begin when the pathologic review has been completed.

10. NCI-064
SERIAL NO.

PROJECT REPORT FORM

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 9,928	1	1	2	1/2	1	1 1/2	
FY 1956	$ 7,297	1	1	2	1/2	1/2	1	

12. BUDGET ACTIVITY

RESEARCH X ADMINISTRATION ___
REVIEW & APPROVAL ___ TECHNICAL ASSISTANCE ___

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

This study is being sponsored by the Laboratory of Pathology, NCI. The Office of Biometry, NIH and the Biometry Section, NCI are providing statistical consultation and clerical service.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

15. NCI-064
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None
No entries for 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4. ______ 5. NCI-065
LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Cancer Illness in Iowa
PROJECT TITLE

7. William Haenszel
PRINCIPAL INVESTIGATOR(S)

8. Samuel C. Marcus
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(A) Objectives: Provide basic data on cancer incidence, prevalence, and mortality in Iowa. Investigate effect of various factors such as age, sex, geographic area within the state and urban-rural status.

(B) Methods Employed: Information on cancer patients seen during the study year (1950) was obtained from virtually every hospital, clinic, laboratory and physician in the state and in certain areas outside the state which were medical centers for Iowa residents.

(C) Major Findings:

(1) With respect to a variety of indices of medical care - survival, stage at diagnosis, length of hospitalization - proportion of cases reported by death certificate only, yet there was no difference between urban and rural experience.

(2) For certain sites there were pronounced urban-rural differences in incidence - lung and bronchus, larynx, buccal cavity, breast, female genital organs. The internal evidence suggested

that these differences could not be accounted for by variations in medical care or diagnostic practices.

(3) In general, the urban-rural incidence patterns in Iowa agreed quite well with the Danish experience reported by Clemmesen.

(D) Significance to Cancer Research: This study contributes data useful for the planning of follow-up studies on the interpretation of urban-rural differentials.

(E) Proposed course of this project for the succeeding calendar year: The study report is now virtually complete and almost ready for publication. After review of the findings by the interested Iowa organization (State Health Department, State Medical Society, medical school) the feasibility of undertaking additional studies to interpret the meaning and significance of the observed urban-rural differentials will be explored.

10. NCI-065
SERIAL NO.

11. ____________
BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 14,591	2	2	4	1	1	2	
FY 1956	$ 1,159	1	-	1	1/8	-	1/8	

12. ____________
BUDGET ACTIVITY

RESEARCH X ADMINISTRATION ___

REVIEW & APPROVAL ___ TECHNICAL ASSISTANCE ___

No entries for 13, 14, 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-066
SERIAL NO.

6. Statistical Studies of Cancer in Pittsburgh Area
PROJECT TITLE

7. William Haenszel and Dr. Antonio Ciocco (these studies are being undertaken in collaboration with the University of Pittsburgh School of Public Health)
PRINCIPAL INVESTIGATOR(S)

8. William Lourie
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(A) Objectives: To pursue a series of intensive cancer morbidity studies in a single area to yield information on factors contributing to unusual incidence for specified sites. The collation of data obtained by a variety of approaches to the same population base will permit stronger inferences to be drawn from the chain of evidence, open the way to designing detailed studies to test specific hypotheses suggested by the evidence, and make possible methodological contributions to field studies of chronic illness in human populations.

(B) Methods Employed: The original conception of a cancer morbidity survey covering three years experience to provide detailed analyses of cancer morbidity by census tract in the initial phase has been modified. Negotiations are under way with the Pennsylvania State Department of Health to make cancer a reportable disease in the Allegheny County area. Under this system hospital cases would be reported to a cancer register and these data supplemented by collection of additional information from hospital records as required and by periodic canvases of physicians in private practice.

PROJECT REPORT FORM

Plans for the succeeding phases of the Pittsburgh studies remain unchanged. The analyses of tracted morbidity data should supply leads for the design of studies to test specific hypotheses, which would open the second phase of the project. Such studies would utilize the unique source of information available locally, such as: the "population laboratory" in the Arsenal Health District and 1% city sample, and the resources of the Department of Occupation Health (in the School of Public Health) in gaining access to records of people working in plants in the Pittsburgh area.

(C) Major Findings: None to report to date.

Much of the personnel time in Pittsburgh has been devoted to the support of projects under the direction of Dr. Gilliam and Dr. McClure.

(D) Significance to Cancer Research: The basic notion of epidemiological studies of a population in depth has never been attempted for cancer on this scale. As mentioned in the objectives, these studies will contribute valuable information on methodology in field studies of chronic illness in human populations.

10. NCI-066
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$14,591	1	2	3	1	1	2	
FY 1956	$19,911	1	2	3	1	2	3	

12. BUDGET ACTIVITY

RESEARCH [✓] ADMINISTRATION __

REVIEW & APPROVAL __ TECHNICAL ASSISTANCE __

No entries for 13, 14, 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-067
SERIAL NO

6. Statistical Consulting and Research Services
PROJECT TITLE

7. Nathan Mantel, Marvin A. Schneiderman, and Samuel W. Greenhouse (transferred to National Institute of Mental Health)
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: Provision of consultative services in statistical design and analysis of experiments, with associated research in statistical methodology

(A) Objectives: The primary objective of this section is to provide assistance in the design, interpretation, and evaluation of experiments conducted by researchers at the National Cancer Institute, (and other institutes, on request). This includes referee services for the Journal of the National Cancer Institute and Public Health Reports, and mathematical assistance for development of theoretical models of biological behavior.

(B) Methods Employed: The assistance described above is accomplished using the standard methods of biometry, statistics, and probability, with the necessary modifications required by the problem at hand. Frequently, standard statistical methods are not sufficient to handle the problem on which assistance is being given, and it becomes necessary for the personnel of the section to originate new methods.

(C) Major Findings: As a service organization, this section primarily assists other researchers in making important biological and medical findings, rather than in making such findings directly. Such assistance is frequently acknowledged in the publication of findings of the

researchers. Examples of the kind of research problems in which assistance is given are shown below.

Occasionally, the nature of the assistance is such as to warrant co-authorship rather than simple acknowledgement. Those are shown below. Also, new statistical methods originated in this office to handle certain problems are sometimes important enough to warrant separate publication.

(D) Significance to Cancer Research: The significance of the contribution of this section to cancer research is best illustrated by the problems in which the section has provided statistical assistance. These include:

(a) Studies of anti-leukemic agents with respect to efficacy and toxicity to host;
(b) Studies on the growth of a transplanted tumor;
(c) Evaluation and development of diagnostic tests for cancer and other diseases;
(d) Radiation effects, and the efficacy of various treatments for radiation damage;
(e) Metabolic studies using radioactive tracers;
(f) Development of synthetic media for tissue culture;
(g) Studies on the genetic and other conditions which modify the growth of transplanted tumors;
(h) Dose-response phenomena in experimentally induced lung tumors (in mice);
(i) Red blood cell survival, and regeneration in disease (leukemia, sickle cell anemia, etc.) and normal states. The use of radioactive tracer techniques in these studies;
(j) Establishment of concepts of drug effectiveness and drug damage;
(k) Investigations of possible synergistic combinations of antileukemic agents;
(l) Study of age of host as a factor in tumor chemotherapy.

(E) Proposed course of this project for the succeeding calendar year: In the coming calendar year, the work of this project will remain substantially unchanged. The principal emphasis will still lie in providing statistical assistance to researchers.

10. NCI-067
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

11.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 41,144	3	~~2½~~ 3	~~5½~~ 6	3	2½	5½	
FY 1956	$ 41,122	3	~~2½~~ 3	~~5½~~ 6	3	2½	5½	

12.

BUDGET ACTIVITY

RESEARCH *

REVIEW AND APPROVAL —

ADMINISTRATION —

TECHNICAL ASSISTANCE —

13. None

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956

14.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH

While there is no essential duplication of work, parallel statistical consulting services are available at the National Heart Institute, the National Institute of Mental Health, and in the Office of The Director, National Institutes of Health.

15. NCI-967

SERIAL NO.

PROJECT REPORT FORM (Cont'd)

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954

Goldin, A., Mantel, N., Greenhouse, S. W., Venditti, J. M., and Humphreys, S. R.: "Effect of Delayed Administration of Citrovorum Factor on the Antileukemic Effectiveness of Aminopterin in Mice." Cancer Research, Vol. 14, No. 1, pp. 43-48, January 1954.

Goldin, A., Mantel, N., Greenhouse, S. W., Venditti, J. M., and Humphreys, S. R.: "Factors Influencing the Specificity of Action of an Antileukemic Agent (Aminopterin). Time of Treatment and Dosage Schedule." Cancer Research, Vol. 14, No. 4, pp. 311-314, May 1954.

Mantel, N. and Robertson, A. H.: "A Comparison of Six Methods of Preparing and Using the Methylene Blue Stain for Bacterial Counts by the Direct Microscopic Method." Journal of Milk and Food Technology, Vol. 17, No. 6, pp. 179-184, June 1954.

Prehn, R. T., Main, J. M., and Schneiderman, M.: "Factors Influencing Tumor Distribution Among the Mammary Glands of the Mouse." Journal of the National Cancer Institute, Vol. 14, No. 4, pp. 895-904, February 1954.

Goldin, A., Mantel, N., Greenhouse, S. W., Venditti, J. M., Humphreys, S. R., and Dennis, D.: "Studies on the Toxicity and Antileukemic Action of 6-Mercaptopurine in Mice." Annals of the New York Academy of Sciences, Vol. 60, Artic.2, 1954.

Goldin, A., Venditti, J. M., Humphreys, S. R., Dennis, D., Mantel, N., and Greenhouse, S. W.: "Factors Influencing the Specificity of Action of an Antileukemic Agent (Aminopterin). Multiple Treatment Schedules plus Delayed Administration of Citrovorum Factor." Cancer Research (in press).

Goldin, A., Mantel, N., Greenhouse, S. W., Venditti, J. M., Humphreys, S. R., and Dennis, D.: "A Quantitative Comparison of the Antileukemic Effectiveness of Two Folic Acid Antagonists." Journal of the National Cancer Institute (in press).

Halperin, M., Greenhouse, S. W., Cornfield, J., and Zalokar, J.: "Tables of Percentage Points for the Studentized Maximum Absolute Deviate in Normal Samples." Journal of the American Statistical Association (in press).

Schneiderman, M. A.: Discussion of paper "Short Term Cultures for Drug Assays: General Considerations," by Pomerat and Leake. Annals of the New York Academy of Sciences, Vol. 58, Art. 7, pp. 1124-1128, November 1954.

Cutler, S. J., Schneiderman M. A., and Greenhouse, S. W.: "Some Statistical Considerations in the Study of Cancer in Industry." American Journal of Public Health, Vol. 44, No. 9, pp. 1159-1166, September 1954.

17. None

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-068
SERIAL NO

6. Cancer Illness in the United States
PROJECT TITLE

7. S. J. Cutler and H. F. Dorn (Office of Biometry, NIH)
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives: Provide basic data on cancer incidence, prevalence, and mortality in the United States. Investigate effect of various epidemiologic factors, such as color, sex, age, geographic region, and economic status.

(B) Methods Employed: Information on cancer patients seen during a specified calendar year obtained from virtually every hospital, clinic, laboratory, and physician in each of ten urban areas surveyed.

(C) Major Findings: Findings published to date are as described in project report for 1954-1955.

During the current year the following aspects of the subject will be analyzed and results published:

(1) Geographic variation in cancer incidence;
(2) Relationship of cancer incidence to economic status;
(3) Changes between 1937 and 1947;
(4) Stage at diagnosis;
(5) Survival experience;
(6) Hospitalization of cancer patients.

(D) Significance to Cancer Research: Provides basic epidemiologic information regarding the incidence of cancer.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

10. NCI-068
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$25,123	1	3	4	1	3	4	
FY 1956	$19,911	1	2	3	1	2	3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

15. NCI-968
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Cutler, S. J. and Haenszel, W. M., "The Magnitude of the Cancer Problem." PHR 69: 333-339, 1954

Dorn, H. F. and Cutler, S. J., "Cancer Illness in the United States. Pub. H. Monograph, in press.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. Office of Associate Director in Charge of Research
LABORATORY OR BRANCH

3.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-2003
SERIAL NO

6. Scientific Planning and Direction
PROJECT TITLE

7. **PRINCIPAL INVESTIGATOR(S)** G. Burroughs Mider
and
Charles Gordon Zubrod

8. None
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION** Associate Director in Charge of Research assumes the responsibility for program in the research area designated by the Director, NCI, and also exercises managerial and administrative functions consistent with the policy for operation of the Institute as determined by competent superior authority. Responsibility for program is shared by Associate Director and Clinical Director, and the latter assumes responsibilities related to care of patients who participate in the research program of the National Cancer Institute. A large part of the work has involved preparation of various documents. Many of these are reports requested by higher echelons of Government, and correspondence with citizens interested in various questions that pertain directly to cancer. Bi-monthly meetings of the laboratory chiefs consider problems of mutual interest to scientists at the National Cancer Institute.

The office facilitates the custodial care operation of the research laboratory area activities relating to general housekeeping, procurement of animal food and bedding, sanitation, distribution of supplies andequipment, property utilization and operation of animal cage equipment sterilization rooms, involving laboratory animal caretakers and laborers.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. Dhc1-200
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$127,364	2	~~27~~ 21	~~29~~ 23	2	~~27~~ 21	~~29~~ 23	-
FY 1956	$130,228	2	~~27~~ 21	~~29~~ 23	2	~~27~~ 21	~~29~~ 23	-

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. NCI - Office of Associate Director in Charge of Research,
LABORATORY OR BRANCH

3. Department of Clinical Pathology Clinical Center, NIH
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-201
SERIAL NO

6. Ultraviolet Television Microscopy
PROJECT TITLE

7. George Z. Williams, M. D.
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Ultraviolet Television Microscopy

Objectives

It is the purpose of this project to develop technics of television ultraviolet microscopy for direct visualization of cytochemical constituents in living cellular material.

Procedure

Instrumentation for the television ultraviolet microscope consists of: an ultraviolet light source; a quartz monochromator and collimating quartz lens system; a research microscope fitted with Grey #V reflecting objective and condenser; and an industrial television camera, power supply, and monitor. The camera lens is omitted and it is fitted with a specially developed ultraviolet sensitive camera tube kindly loaned for this research by Dr. L. E. Flory of the David Saranoff Research Laboratories of the RCA. The morphologic pattern of the ultraviolet absorption characteristics of living cells is visualized directly on the television monitor screen. With a Polaroid-Land paper film, a photographic record may be made, developed, and inspected immediately.

The NIH Instrument Section assisted in designing, and built an excellent time-lapse control for recording processes in the living cell by time lapse cinematography. I designed and fabricated a camera shutter to synchronize the shutter opening with the scanning time of the television screen, thus eliminating the bothersome moving black and white bars otherwise present in the picture.

NCI-201
Serial No.

PROJECT REPORT FORM (Cont'd)

By utilizing a specially designed oscilloscope, one of the 525 raster lines of the television screen is selected and analyzed and photographically recorded. This tracing provides a pattern of relative absorption densities and their proportions in the cell path traversed by the selected line.

Major Findings

Calibration and Standardization of the Instruments

The major portion of the work during the past year has been devoted to setting up the instruments, adjusting their operation, and more recently, in standardization and calibration of the instruments in order to provide more accurate information of the absorption characteristics of cellular material.

The calibration of the oscillographic record is based on the vertical voltage deflection (image density) and its duration in microseconds (diameter of dense image). In order to determine the reproducibility and the linearity of the television screen record of cell structure in terms of ultraviolet absorption, the density pattern provided by a direct ultraviolet photograph is compared with the oscillographic record. A constant standard of ultraviolet absorption of varying degrees is required to standardize measurements and determine reproducibility. Present experiments are designed to provide a useable standard absorption slide.

Significance to Cancer Research

Preliminary Cytochemical Studies

The following cytochemical studies have been started, utilizing the technic described above and the data accumulated will contribute to general basic understanding of the constitution and metabolism of cancer cells.

1. The distribution and ultraviolet absorption of nuclear chromatin material in living cells.

2. Tetrazolium salts reduced to their respective formazans by certain dehydrogenases can be visualized within cells in very small concentrations by their ultraviolet absorption at 290 to 300 mμ. Krebs 2 free tumor cells and our HS1 free tumor cells reduce certain tetrazolium derivatives without substrate. Twenty tetrazolium derivatives of varying properties have been provided by Dr. Pierce, Professor of organic chemistry at Richmond University. These were synthesized with the idea of attempting to change their chemical properties with the possibility in mind that they would thus be reduced by specific enzymes. Their reaction in cancer cells is being recorded.

3. Ultraviolet absorption morphology is being recorded ~~from~~ in fresh blood and marrow specimens from patients with leukemia.

PROJECT REPORT FORM (Cont'd)

Proposed Course of Project

After completion of the standardization and calibration of the instruments and preliminary records of normal-type cells, this project will accumulate data and modify and augment the technics to include the following:

1. Time lapse motion picture photography of living intracellular processes which show alteration of tetrazolium to formazan and other similar cytochemical changes as they are developed.

2. Record ultraviolet absorption changes of cells during the aging process, injury by ultraviolet, x-ray and chemotherapeutic agents, fixation, death, and virus infection.

3. Accumulate ultraviolet absorption, morphological data on human cell material, chiefly; white blood cells of the peripheral blood, bone marrow, and cells from the cervix before and after different types of treatment for cancer.

PROJECT REPORT FORM (Cont'd)

10. MC1-201
SERIAL NO.

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11. **BUDGET DATA:**

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$12,561	0	$1\frac{1}{2}$	$1\frac{1}{2}$	$\frac{1}{2}$	$1\frac{1}{2}$	2	
FY 1956	$15,274	0	2	2	$\frac{1}{2}$	2	$2\frac{1}{2}$	

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12. **BUDGET ACTIVITY:**

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

(a) David Saranoff Research Lab., RCA, Princeton, New Jersey; Special tubes.

(b) University of Richmond, Department of Chemistry, Dr. John S. Pierce, Professor; A.G. Richardson, Graduate Student; Mr. Hansrote, Graduate Student; supported by $2400 fellowship through Oncology Department, Medical College of Virginia by their Institutional Grant from the American Cancer Society; synthesized 20 tetrazolium derivatives.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Endocrinology
LABORATORY OR BRANCH

3. Environmental Cancer
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-202
SERIAL NO

6. Investigations on Carcinogenic Aromatic Amines ,including Azo-Dyes, Triphenylmethane Dyes and Antioxidants and their Metabolites
PROJECT TITLE

7. W.C.Hueper,C.Grogan,D.Cole
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION** An attempt will be made to isolate and identify the metabolites of a number of food-and industrial dyes and rubber antioxidants which are derivatives of naphthylamine,benzidine, or triphenylmethane from various portions of the alimentary tract of dogs,rabbits and rats and from the urine of these species and of man. Metabolites with unknown carcinogenic properties will be tested by bioassays on animals.

Methods: The chemicals to be tested shall be introduced into isolated parts of the stomach and intestine of dogs. The reaction products contained in the gastric or intestinal secretion acting upon the chemicals will be collected in plastic cups and subjected to chemical and physical analysis. An attempt will be made to identify metabolites by utraviolet and infrared spectrographic and spectrophotometric methods and,if possible,by specific color reactions to be developed.

Similar experiments may be performed on rabbits and rats using ligated portions of the alimentary tract.

Urine will be collected from dogs and rabbits given the various chemicals by mouth,so as to obtain data on the urinary metabolites. After the methodology on the identification of metabolites has adequately been developed,human urine will be collected, and concentrated by thermo-drying or vacuum-drying and studied for specific metabolites from the various food-dyes.

The testing of metabolites will be done by subcutaneous implantation of lard or paraffin pellets and by the deposition of similar material into the urinary bladder of rats.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

The project at the present time had progressed to the preparation of isolated gastric and intestinal pouches in dogs and the development of techniques for collecting the secretory juices from these pouches.

Significance to Cancer: The use of food-drug-and cosmetic dyes subjects the general population through their entire lifetime to contact with chemicals which if split and metabolized properly by the body may give rise to the production of carcinogenic metabolites of the naphthylamine and benzidine variety. A number of triphenyl- and biphenylmethane dyes used for coloring foods have been found to be carcinogenic in rats, and thus constitute potential human carcinogens. There is moreover the fact that a great number of workers have active and intense contact with the less purified commercial dyes of similar chemical constitution. Since human and/or animal experience has shown that some constituents of these dyes have produced bladder cancers in man and animals and a few also cancers of other organs, such as especially the intestinal tract in animals, a competent study of potential human cancer hazards through such contacts and from various sources is indicated.

PROJECT REPORT FORM (Cont'd)

10. Ncl-202
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	~~13,000~~ $17295	1	1	2	1/2	1/2	1	
FY 1956	~~41,000~~ $45,553	3	3 1/3	6 1/3	3	3 1/3	6 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

15. NCI-202
SERIAL NO.

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16. **PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:**

W.C.Hueper,Occupational Bladder Cancer
Proc. 2nd Nat.Cancer Conf. Cincinnati,1952,p.361-375

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17. **HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:**

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Endocrinology
LABORATORY OR BRANCH

3. Environmental Cancer
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-203
SERIAL NO

6. Experimental Studies on Carcinogenic Properties of Macromolecular Polymerized Compounds, Particularly Plasma Extenders
PROJECT TITLE

7. W.C.Hueper
PRINCIPAL INVESTIGATOR(S)

8. NONE
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION** Objective:

ecause of the production of cancers in mice and rats by the parenteral introduction of various synthetic macromolecular polymerized substances used as plastics and resins by Turner; Druckrey and Schmähl; and Oppenheimer et al., it appeared interesting and essential to study further the phenomenon of "polymer cancers" by the use of polymers of various molecular size and shape and to ascertain at the same time whether or not certain plasma extenders, namely polyvinyl pyrrolidon and dextran, which are chemically similar to some of the established carcinogenic polymers, share this property of carcinogenicity.

Methods: For the purpose of the investigation ten different types of dextrans differing among each other in size and shape of the molecule and six different type of polyvinyl pyrrolidon were obtained, ranging in molecular weight between 10,000 and 300,000.

The dry materials were implanted into the subcutaneous tissue and into the peritoneal cavity of mice and rats, and, whenever adequate amounts were available, injected intravenously into rabbits.

Similar deposits are prepared with several chemically related polymers not in use as plasma extenders, such as various starches, polyvinyl alcohol, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, i.e. chemicals for which industrial exposure to dust and spray exists.

Periodic hematologic studies are made on the animals intravenously injected with the macromolecular materials. All animals are allowed to die spontaneously so as to observe possible late effects.

Preliminary Findings: Several rats injected subcutaneously with PVPs developed medullary white masses in the pleural space, while rats intraperitoneally injected with soluble starch developed abdominal tumors

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

Significance to Cancer: From a fundamental scientific viewpoint studies on polymer cancers may contribute to our knowledge of the mechanism of cancerigenesis since the action mechanism of polymers, i.e. their combination with cellular proteins(?) may form a link between the known carcinogen-protein complexes demonstrated for 3,4-benzpyrene and several aromatic azo compounds of the butter yellow group on the one hand and the "radiomimetic effects" of other carcinogenic agents. They may give us also information on the role of molecular size and shape in such matters.

Since the synthetic plasma extenders have extensively been used in man without proper testing for potential carcinogenic properties and since huge amounts of polymerized chemicals are used for numerous purposes in industry large numbers of workers have active contact with such agents, while the general public becomes exposed to them in the form of medical protheses and implants, as wrapping material of foodstuffs and of ingredients of food.

Proposed Course of the Project: Since the project was started during the past year it shall take at least another, if not two years before data will be available suitable for reliable interpretation.

PROJECT REPORT FORM (Cont'd)

10. Mcl-203
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	~~11,000~~ $13,640	1/3	2	2 1/3	1/3	2 ~~1/3~~	2 1/3	
FY 1956	~~15,000~~ $18,592	2/3	2 1/3	3	2/3	2 1/3	3	

12. BUDGET ACTIVITY:

RESEARCH ☒ DMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Endocrinology
LABORATORY OR BRANCH

3. Environmental Cancer
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-304
SERIAL NO

6. Experimental Investigations on Petroleum Substitutes and Synthetic Liquid Fuels
PROJECT TITLE

7. W.C.Hueper ,H.J.Cahnmann
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION** Objectives:

The project was undertaken with cooperation of the Bureau of Mines for ascertaining whether crude oils and distillation fractions of American shale oil and synthetic coal oils manufactured according to the techniques of Bergius and of Fischer-Tropsch possess carcinogenic properties and contain known carcinogenic hydrocarbons which may account for the total or partial carcinogenic properties of such oils.
The first report dealing with bioassays of various fractions of these oils obtained in pilot operations was published in Arch.Industr.Hyg. & Occup.Med. 8:307-327,1953(Hueper). During the past year bioassay work was conducted on large scale production samples of the Bergius and Fischer-Tropsch oils and on various fractions of shale oil obtained by a chromatographic fractionation of shale oil and including fractions without demonstrable 3,4-benzpyrene content. The chemical studies were directed at a qualitative and quantitative evaluation of the benzpyrene content of numerous fractions obtained from chromatographic fractionation of a sample of crude shale oil(Cahnmann)(see attachment).

thods: The bioassay of the eight fractions so far tested was made by
ale making in weekly intervals 6 injections of a solution of the fraction
ls (20%) in olive oil into the thigh muscle of C57 black mice. After
12 months so far 4 infiltrating tumors of the hip were seen in animals given three of the fractions,suggesting the presence of other carcinogens in shale oil in addition to 3,4-benzpyrene.

rgius Nine different fractions of Bergius oil covering coke,various
ls grades oils and gasolines were painted on the skin of mice and rabbits,
and injected diluted with tricrapylin into the thigh muscle of rats.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-204

Papillomas and carcinomas were obtained in some of the mice painted with the heavy fractions but not with the light and gasoline fractions. Tumor formation was less pronounced in rabbits given cutaneous applications of the heavy fractions.

The intramuscular injection of these fractions into rats,on the other hand,resulted in tumor formation in the thigh of rats given the lighter fractions exclusive of gasolines,while the heavy fractions did not elicit any tumors.
This different species specific reactivity to the various Bergius oil fractions is of distinct interest in interpreting results obtained in screening procedures of suspected carcinogenic chemicals. Since the majority of the rats are still alive,final conclusions cannot be drawn. Since Bergius oils are largely aromatic carcinogenic properties of some fractions has to be expected.
Significance to cancer research: Apart from the demonstration of carcinogenic properties for some of the various Bergius coal oils,these ob servations are of importance for practical reasons since during recent years several large American industrial concerns have erected plants for the direct hydrogenation of coal and therefore may have to face skin and lung cancer hazards for their employees. The Bureau of Mines had already one compensation claim by a foreman employed in their former Bergius oil plant at Louisiana,Mo.

Fischer-Tropsch Oils Five different fractions of Fischer-Tropsch products obtained from a large scale operation at Louisiana,Mo. from the Bureau of Mines were applied to the skin of mice(C57 black) and injected intramuscularly into the thigh of rats. Suspected tumors of the skin were obtained in only three of 50 mice painted with the Diesel oil fraction. None of the rats developed any tumors at the site of injection,although several showed abdominal tumors. Skin painting in rabbits were negative.

Significance to cancer Research: The predominantly aliphatic nature of the Fischer-Tropsch products made a distinct carcinogenic potency of these waxes,greases and oils an unlikely possibility. The experiments on these industrial products provide confirmation of this concept. It appears therefore that among the two types of synthetic coal oils,the Fischer-Tropsch oils are safer to produce and use from a carcinogenic viewpoint.

Future Course of the Project: This project shall be terminated after the last surviving animals have died and have been analyzed.

10. Wel-204
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	~~8,000~~ $13,239	2/3	1 1/3	2	2/3	~~1/13~~ 1 1/3	~~5~~ 2	
FY 1956	0	0	0	0	0	0	0	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:
Bureau of Mines furnished oils and various chemical data and manufacturing information on these oils.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Endocrinology Branch
LABORATORY OR BRANCH

3. Environmental Cancer
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-205
SERIAL NO

6. Experimental Studies in Metal Cancerigenesis
PROJECT TITLE

7. W.C.Hueper
PRINCIPAL INVESTIGATOR(S)

8. Dr.H,Cahnmann;Dr.C.H.Grogan,Mr. W.W.Payne
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION** The objective of this project:To produce cancers in various species of animals by parenteral introduction of various metals and minerals(chromium,chromite ore,nickel,beryllium,arsenic, uranium,asbestos) and thereby provide experimental support to observations on occupational respiratory cancers made among members of certain occupational groups; to determine the distribution,metabolism and interaction of such agents with tissue components and biologic media in in vitro and in vivo experiments;to develop microanalytic methods for the reliable determination of minute amounts of these agents in biologic media.

Methods: Five different lines of investigation were followed.

1. Bioassay of the various agents for carcinogenic properties through parenteral introduction(subcutaneous,intramuscular,intraosseous,intrapleural,intraperitoneal,intravenous,intra-nasal sinus) and in part by inhalation of dust(chromite ore,nickel).
2. Immunochemical studies for ascertaining the possible development of metal specific antibodies in experimental animals injected with chromium acetate-egg albumin and chromium acetate-blood plasma antigens as well as in chromate manufacturers with and without cancer of the lung.
3. Biochemical investigations of in vitro type on the formation, nature and stability of chromium salt-protein conjugates by electrophoretic and dialysis techniques using egg albumin and human plasma as the proteinic medium and Cr^{III} and Cr^{IV} compounds.
4. Analytical studies :On the behavior of chromium compounds in the physiological pH range,the formation of chromium olates and their effects on the dialysis of chromium salts;on the degree of chromium solubility of chromite ore;on the development of microanalytic methods.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

Major Findings:

1. Intraosseous and subcutaneous implantation of nickel into rats caused cancers of various types in about 30 per cent of the animals used, osteogenic sarcoma appeared in one rabbit 4 years after an intrafemoral implantation of nickel. No tumors were obtained in mice, guinea pigs, and dogs. One rat developed a pancreatic insuloma after an intrafemoral injection of nickel.
   The parenteral deposition of chromium and chromite ore did not result in tumor formation in mice, guinea pigs, rabbits and dogs. Rats in a few instances showed local sarcoma formation after intrapleural and intrafemoral introduction of chromium, revealed two papillary adenomas one with squamous cell carcinomatous transformations in 2 out of 20 intravenously injected animals, and insulomas in one intrafemorally and 2 intraperitoneally injected rats. Pulmonary adenomas in rats are very uncommon, and insulomas in rats have not been reported before.
   The experiments with beryllium, arsenic and asbestos on rats were essentially negative for chemospecific tumor formation.
2. While precipitation tests performed on chromium acetate-plasma protein complexes with antisera of sensitized rabbits gave rather consistent chromium-specific reactions, those using serum of chromium workers as antiserum were sometimes in agreement with the exposure conditions of the donors of the antiserum, at other times quite erratic, apparently because of instability of the antigen.
3. The preparatory fundamental studies on the interaction of trivalent and hexavalent chromium salts with proteins showed that at pH 7.35 human plasma binds 2 to 3 times as much Cr^{VI} as did egg albumin. Cr^{III} is bound by egg albumin and plasma protein at pH 7.35 to approximately equal degrees and bindings appears to increase with time of contact.

4. Trivalent chromium compounds form olates and polynuclear olate and ox-olate complexes, approaching the size of colloids. A small fraction of chromium in chromite ore is water soluble and therefore capable of biologic action. Microanalytic techniques perfected permit the assay of from 0.1 to 5 micrograms of chromium in urine, plasma, serum and other protein solutions, paper strips from epectrophoresis and various buffer solutions.

gnificance to Cancer: The highly excessive liability of chromate manufacturers and chromium pigment handlers to lung cancer, the excessive incidence of nasal cavity, nasal sinus and lung cancer among nickel refinery workers, of lung cancer among certain types of arsenic and asbestos workers and, particularly, among radioactive ore miners provide the practical importance for the project, and point to the potential presence of similar cancer hazards among large worker groups and parts of the general population exposed to the same carcinogenic metals.

roposed Course of the Project: Exposures to nickel and chromite ore dust mixed with powdered lime stone so as to imitate exposure conditions existing near roasters will be continued, using rats, guinea pigs and rabbits. Dogs and rabbits with intravenous and intrafemoral implantations of chromium, nickel, uranium and arsenic will be observed for tumor formation during the coming year.

NCI-205

The immunochemical studies will be continued in cooperation with the Mutual Chemical Company,Maltimore,Md. which will furnish blood of chromate manufacturers. New antigens will be prepared using identified fractions of plasma proteins to be supplied by the Baxter Co.

One larger series of rats with intrafemoral uranium implantations made during the past year shall be observed for tumor developments. A second series with intrapleural uranium deposits will be subjected to the same regimen.

Chromite ore roast suspended in tallow was deposited intramuscularly and intrapleurally in two series of rats of 30 animals each,so as to test whether or not some early roasting products of chromite ore possess carcinogenic properties. None of these rats has died as yet.

PROJECT REPORT FORM (Cont'd)

10. Mcl-205
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$28,585 ~~20,000~~	1 2/3	2 2/	4 1/3	1 2/3	2 2/3	4 1/3	
FY 1956	~~18,000~~ $21,684	1	2 1/	3 1/3	1	2 1/3	3 1/	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

5. NCI-205
SERIAL NO.

6. **PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:**

Hueper,W.C.,Experimental Studies in Metal Cancerigenesis. VI. Tissue Reactions in Rats and Rabbits After Parenteral Introduction of Suspensions of Arsenic,Beryllium,or Asbestos in Lanolin. J.Nat.Cancer Inst. 15:113-128,1954.
Hueper,W.C.,Experimental Studies in Metal Cancerigenesis. IV. Cancer Produced by Parenterally Introduced Metallic Nickel. J.Nat.Cancer Inst. in press.
Hueper,W.C.,Environmental Lung Cancer. Industr.Med. & Surg. 23:463-467 1954.
Hueper,W.C.,Lung Cancer and the Tobacco Smoking Habit. Industr.Med. & Surg. 23:13-19,1954.
Hueper,W.C.,Environmental Lung Cancer, Proc. 1st.National Cancer Conference of Canada,1954,Academy Press,in press.
Hueper,W.C.,Recent Developments in Environmental Cancer. Arch.Path. 58: 360-399;475-523;645-682,1954.
Grogan,C.H. and Oppenheimer,H.,Experimental Studies in Metal Cancerigenesis.III. Behavior of Chromium Compounds in the Physiological pH Range. J.Am.Chem.Soc.,1935. in press.
Grogan,C.H. and Oppenheimer,H.,Experimental Studies in Metal Cancerigenesis. V. Interaction of Cr^{III} and Cr^{VI} Compounds with Proteins. Arch.Biochem. & Biophys. in press.
Grogan,C.H. and Roboz,E.,Simple Apparatus for Concentrating Biological Fluids of Low Protein Content. J.Lab.Clin.Med. in press.
Hueper,W.C.,Occupational Cancer: A Challenge.Health News 31:4-16,1954.
Hueper,W.C.,Medicolegal Aspects of Cancer. Am.J.Clin.Pathol.in press.
Hueper,W.C. Environmental Causes of Lung Cancer. Publ.Health Rep.inpres
Hueper,W.C. An Analysis of the Environmental Causes of Lung Cancer Proc.Am.Pharm.Manuf.Ass.Meeting,New York,1954,in press.
Hueper,W.C. Environmental Cancer of the Lung. Acta Union Internat. Against Cancer,in press.
Hueper,W.C.,Considerations for the Selection of Chemicals for Carcinogenic Screening. Arch.Industr.Hyg.&Occ.Med. in press

7. **HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:**

Chairman,Section of Occupational Pathology,International Congress of Clinical Pathologists,September,1954,Washington,D.C.
Chairman,Committee on Cancer Prevention,International Union Against Cancer
Member,Committee on Carcinogenic Agents Research,International Union Against Cancer

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6. Publications continued:

Hueper,W.C.,Occupational Cancer Hazards. Safety Standards(**Department of Labor**) and Proc.40th Conf.Internat.Ass.Industr.Acc.Boards and Comm. in press.
Kotin,P. and Huper,W.C.,Relationship of Industrial Cancer in the General Population. Publ.Health Rep. in press.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Endocrinology
LABORATORY OR BRANCH

3. Environmental Cancer
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. EC-206
SERIAL NO

6. Experimental Studies on Industrial Water Pollutants
PROJECT TITLE

7. W.C.Hueper
PRINCIPAL INVESTIGATOR(S)

8. W.W.Payne
C.C.Ruckhoft(Robert Taft Sanitary Engineering Center,Cincinnati,Ohio)
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION** Since various types of carcinogenic wastes(ship fuel oil,effluents of oil refineries,chromate manufacturing plants, and arsenic ore smelters,radioactive mater)enter public waters which later may be used for drinking water supplies or become accumulated in edible marine animals,the present project was devised for ascertaining whether carcinogenic material might be extracted from raw and processed waters and whether such matter might be isolated from edible shellfish(crabs, shrimps) and mollusks(clams,oysters),since it had been shown that barnacles apparently concentrate 3,4-benzpyrene from ocean water polluted with ship fuel oil known to contain carcinogenic hydrocarbons.

Methods: Four different activated carbon adsorbates prepared from polluted raw water and/or processed water were used. One of them was obtained from oil refinery effluents having a catalytic cracking unit, a second came from the ship canal into which these effluents were released,a third was collected from a river heavily contaminated with wastes of a variety of chemical plants,and the fourth was processed river water adsorbate. The tarry materials were painted on the skin of mice (C57 black),twice a week for 12 months.

Major Findings: Mice painted with the adsorbates containing the effluents of the oil refinery developed in a few instances papillomas and carcinomas,attesting the presence of carcinogenic substances in these polluted bodies of water.

Significance to Cancer: The observations furnish additional evidence indicating the spread of industry-related carcinogenic material into the human environment and into articles of daily human consumption. Such observations may be valuable in the establishment of industries and in controlling the release of harmful and carcinogenic pollutants into waters of public ownership.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

Proposed Course of Project: A carbon adsorbate obtained from the effluents of an oil refinery engaged exclusively in thermodistillation of petroleum products is at present studied by skin painting of mice.

Crabs collected from oil polluted parts of Baltimore harbor and oysters to be obtained from oil polluted waters of the harbor of Norfolk,Va. will first be studied spectroscopically for the presence of known carcinogenic hydrocarbons(Dr.H.Cahnmann). If these studies should show carcinogenic material,quantitative bioassays may be attempted,so as to ascertain an approximate idea of the potential hazards which may be related to their human consumption and handling.

PROJECT REPORT FORM (Cont'd)

10. M-206
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	~~7,000~~ $8,394	1/3	1	1 1/3	1/3	1	1 1/3	
FY 1956	$8,446 ~~7,000~~	1/3	1	1 1/3	1/3	1	1 1/3	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Robert Taft Sanitary Engineering Center which furnished the carbon adsorbates as well as the chemical analyses.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-206
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Hueper, W.C. and Ruchhoft, C.C., Carcinogenic Studies on Adsorbates of Industrially Polluted Raw abd Finished Water Supplies.
Arch. Industr. Hyg. & Occup. Med. 9:488-495, 1954

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

12-31-54 PROJECT REPORT FORM

1. N.C.I.
INSTITUTE

2. Endocrinology
LABORATORY OR BRANCH

3. Environmental Cancer
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-207
SERIAL NO

6. Detection and quantitative determination of benzo[a]pyrene in American shale oil.
PROJECT TITLE

7. H. J. Cahnmann
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION** This project is part of a series of investigations dealing with aromatic hydrocarbon carcinogenesis.

Objectives: The objective of this project is to investigate the chemical nature of the carcinogenic constituents of American shale oil. As a first step in this direction a qualitative and quantitative evaluation of benzo[a]pyrene in a typical sample of Colorado shale oil was to be made.

Methods employed: The crude shale oil is fractionated by vacuum destillation followed by a series of chromatographic separations on various adsorbents. After this extensive purification, benzo[a]pyrene can be detected and quatitatively determined by means of absorption spectrophotometry and/or fluorescence spectrophotometry. The latter method has been refined and thus made so sensitive that considerably more accurate and precise benzo[a]pyrene determinations can be made than with the methods reported by other investigators. A typical sample of N.T.U.-shale oil was found to contain between 0.003 and 0.004 mg. benzo[a]pyrene per 100gm. crude oil. This is considerably less than the amount of benzo[a]pyrene found in coal tar (ca. 0.3 – 0.8 %), somewhat less than the amount found in soot(ca. 0.03 %) and considerably more than the amount roughly estimated to be present in cigarette tar (ca. 0.00002 %).

Significance to cancer research: Shale oil represents a cancer hazard to workers engaged in its manufacture and processing. In order to make the institution of safeguard measures possible a better knowledge of the nature of the carcinogenic constituents of shale oil is required. Furthermore, the methods developed for the accurate and precise determination of benzo[a]pyrene in shale oil is no doubt applicable to other complex mixtures containing trace amounts of benzo[a]pyrene (e.g. air and water pollutants or cigarette tar).

Proposed course of project: 1) Bioassays under the direction of Dr. W. C. Hueper are partly under way and partly to be started with the aim of determining whether potent carcinogens other than benzo[a]pyrene are present in American shale oil.
2) The knowledge gained and some of the methods worked out in the course of this investigation will be applied to the study of carcinogens possibly present in sea food collected in (PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION) contaminated water.

PROJECT REPORT FORM (Cont'd)

10. Mcl-207
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$6,216	1	—	1	2/3	—	2/3	0
FY 1956	$ 0	—	—	—	—	—	—	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

15. 244-209
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Detection and Quantitative Determination of Benzo[a]pyrene in American Shale Oil

To be submitted for publication in about two weeks.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

HJCahnmann
12-31-54

PROJECT REPORT FORM

1. N. C. I.
INSTITUTE

2. Endocrinology
LABORATORY OR BRANCH

3. Environmental Cancer
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-208
SERIAL NO

6. Microdetermination of Chromium in various biological media
PROJECT TITLE

7. CH. H. .Grogan and H. J. Cahnmann
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION** This project is part of a larger project; Studies in metal carcinogenesis.

Objectives: The objective of this project is to develop a method for the accurate and precise routine determination of traces of chromium in a variety of biological media, such as buffer solutions, plasma and other protein solutions, urine, filter paper strips from paper electrophoresis experiments, etc.–. Such a routine method was needed for other projects in the metal cancer series, particularly for the one dealing with the binding of chromium to proteins(see Ch. Grogan and H. Oppenheimer).

Method~~s~~ employed: The sample is dry or wet ashed, the ash is oxidized in order to transform trivalent into hexavalent chromium which is then determined spectrophotometrically in the form of the colored complex which it forms with 1,5-diphenylcarbohydrazide.

Major findings: The method is applicable to a large number of biological media. It combines simplicity with a relatively high degree of accuracy and precision. It is not applicable to samples containing chromium in acid-insoluble form (chromite ore), nor to samples that are very rich in iron (e.g. blood).

Significance to cancer research: Without a rapid routine method of this sort (not heretofore available) it would be almost impossibe to carry out the other projects dealing with chromium carcinogenesis (unless they were done with radioactive chromium). The method will no doubt also be a valuable tool in the hands of other investigators who study the metabolism of traces of chromium.

Proposed course of project: It is intended to seek procedures that will widen the scope of application of the method.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. NCI-208
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$12,699	2	1	3	1 1/3	1	2 1/3	0
FY 1956	$4,865	1	1	2	1/3	1/3	2/3	0

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

15. 701-208
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The Microdetermination of Chromium in Small Samples of Various Biological Media
Analytical Chemistry, in press

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Lab. of Chemical Pharmacology
LABORATORY OR BRANCH

3. Office of the Chief
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-350
SERIAL NO.

6. Study of pharmacology of tumor necrotizing agents.
PROJECT TITLE

7. Murray J. Shear
PRINCIPAL INVESTIGATOR(S)

8. A. Perrault, S. N. Pradhan, D. Rall, M. Belkin, I. Wodinsky and M. Kelly;
OTHER INVESTIGATORS Prof. Paul Gyorgy and Dr. Georg Springer (U. of P.)

9. PROJECT DESCRIPTION

Objectives:

(1) Better understanding of the mechanism of action of a number of tumor necrotizing agents as to both tumor damaging action and undesirable side effects, and the effects of these agents on serum polysaccharide levels; and (2) Development of new sources of different active polysaccharides from plants and normal and tumor-bearing animals.

Methods Employed: Standard biochemical, physiological and pharmacological methods; a new method developed here for obtaining blood pressure directly from the carotid artery of the mouse; novel techniques for isolation of tumor-active polysaccharides.

Major Findings:

(1) The effect of a variety of pressor and depressor drugs on arterial blood pressure in the mouse was studied with a novel technique developed in this Laboratory for the purpose. Both normal and tumor-bearing mice were used. These well known drugs were found to affect blood pressure in the mouse as they did in larger mammals.

When a series of tumor-necrotizing drugs was studied in the same way, no support was obtained for the alleged explanation that an antecedant hypotension was the cause of tumor correlation. A correlation between tumor-necrotizing

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

potency and reduction of blood pressure was not found when the pressure was measured directly in the carotid artery.

Analogous data in normal and tumor-bearing rabbits yielded similar findings.

(2) Induction of hemorrhagic necrosis in tumors is related to production of Shwartzman phenomenon. The latter has been studied to help illuminate mechanism of action of the former. It was found that an anticoagulant (Tromexan) and a sympatholytic drug (N-ethyl-N-2 bromoethyl-1-naphthylene-methylamine) inhibited the local Shwartzman reaction induced with a tumor-necrotizing polysaccharide.

(3) Pyrogens. In view of the increasing clinical use of parenterally-injected solutions of many types, assay for pyrogenic activity of such solutions is increasing in importance. The World Health Organization, thru its Expert Committee on Biological Standardization, has requested 1000 mg. of our polysaccharide from S. marcescens for study of its suitability "as a reference preparation for pyrogens. This material was provided to WHO, which has been distributing it this year to various institutions throughout the world, including 2 mg. to the Microbiological Institute of the NIH.

The tumor-necrotizing polysaccharide is also a powerful pyrogen. A quantitative estimation was made in this project of the development of tolerance to the febrile action following repeated administration of this agent in rabbits.

(4) Prior to administration of several tumor-affecting drugs to patients by our clinical colleagues, the drugs were examined for toxic effects on mucous membranes in larger laboratory animals following topical administration.

(5) The isolation of polysaccharides was extended to a variety of plant tissues, and of animal tissues, including tumors. As expected, most were inactive against S37; however, a most interesting series of them had tumor-necrotizing potency. Data have begun to be obtained on their other biological activities such as pyrogenicity and Shwartzman activity. In this connection it is significant that the polysaccharide obtained from the abdominal skin of the normal rabbit not only is tumor-active, but also possesses preparative and provocative potency for the local Shwartzman reaction.

At the initiative of Prof. Paul Gyorgy (U. of P.) and of Dr. Georg Springer (U. of P. and Armed Forces Grad. Med. School) a joint study of these polysaccharides for blood group activity and for bifidus factor activity was begun. Even in the early stages of this work, interesting findings were obtained which have clinical implications.

(6) A critical examination is being conducted of the methods for estimating polysaccharides in blood serum. A satisfactorily reproducible technique has been accomplished, and the method applied to animals with and without tumors, and with or without treatment with bacterial polysaccharide. The effects of tumor and of treatment on the blood levels has been ascertained, and further data are being accumulated.

Significance to cancer research: A knowledge of the diverse actions, and of the mechanisms of these actions, of known tumor necrotizing drugs, aids in development of a rational approach to cancer chemotherapy, and is useful in the search for agents necessary for clinical investigation.

Proposed course of project: These lines of research will be continued, and will be modified from time to time so as to bear as directly as possible on the target of development of drugs for the clinic with maximum potency and minimum toxicity.

10. NCI-750
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$95,226	4*	11	15*	4*	11	15*	
FY 1956	$106,234	4*	13	17*	4*	13	17*	

* Includes 1 Visiting Scientist

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Prof. Paul Gyorgy, U. of Penn.

Dr. Georg Springer, U. of Penn. and Armed Forces Grad. Med. School.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

15. NCI-250
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. Leiter, J., Perrault, A., Hartwell, J. L., Kline, I., and Shear, M. J.: Negative Results with Diphenylethylamines in Producing Damage in Sarcoma 37. Cancer Research, Suppl. No. 2 (in press).

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Murray Shear's work received the following recognition:

1. His polysaccharide was selected by the Expert Committee on Biological Standardization of WHO for study of suitability as an international standard of pyrogenicity.

2. He was appointed Chairman of the new Chemotherapy Committee of the International Cancer Research Commission, and was asked to organize and activate it.

3. The 6th International Cancer Congress in Brazil invited him to participate in a symposium on Carcinogenesis, and provided first-class, round-trip plane transportation.

(next page)

4. Chairman of a pre-clinical session of a Conference on 6-Mercaptopurine, under the auspices of the N.Y. Academy of Sciences in April.

5. Chairman of a Symposium on Carcinogenesis under the auspices of the Division of Medicinal Chemistry of Amer. Chem. Soc., and of Amer. Cancer Society, in New York in September.

6. Lectured on Experimental Cancer Chemotherapy at 7th Cancer Day of Rhode Island State Medical Society in Providence in October.

These activities, and participation (by invitation) in other scientific conferences, were performed at no expense to Government; the organizations concerned defrayed the costs.

7. Macy Foundation invitation to participate for oncology, in a 5-year series of Conferences on Polysaccharides, beginning in April 1955 (expenses paid by the Foundation).

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Lab. of Chemical Pharmacology
LABORATORY OR BRANCH

3. Organic Chemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-251
SERIAL NO.

6. Isolation, synthesis and determination of structure of chemical agents useful in damaging animal or human tumors, or in studying the pharmacologic action of such drugs.
PROJECT TITLE

7. J. L. Hartwell
PRINCIPAL INVESTIGATOR(S)

8. A. Schrecker, D. Vivian, R. Ross, J. Wood, J. Leiter, D. Fitzgerald, A. Perrault and M. J. Shear
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To forge novel chemical materials which will be useful in controlling animal or human tumors, or in studying the pharmacologic mechanism of action of such drugs.

Methods Employed: Chemical compounds are either isolated from plant or animal tissues, or synthesized. Methods of isolation and purification depend entirely on the particular tissues used, and have included solvent extraction, chromatography, and use of ion exchange resins. Methods of synthesis run the gamut of organic chemistry, depending on the type of compound desired. When compounds of unknown structure are isolated, most recent methods of organic chemistry are used to elucidate its structure, including degradative and synthetic chemical reactions, and ultraviolet and infrared spectroscopy. Fate and distribution of drugs given to animals are studied with tracer atom techniques utilizing radioactivity apparatus. For the identification of metabolic products of those drugs, techniques have been worked out involving paper chromatography and paper electrophoresis.

Major Findings:

A. Stereochemistry of Lignans. The configuration of podophyllotoxin has been determined and related to that of most of the other lignans. The structures and configurations of several new lignans have been determined. The steric requirement for activity in damaging tumors was found.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-251

B. Synthesis of Biologically Active Lignans. A number of tumor-active, water-soluble derivatives of podophyllotoxin and the peltatins to facilitate biological study have been created. New methods for the preparation of some pyridine derivatives were discovered.

C. Synthesis of Improved Vital Stains. A study of the commercial phenazine dye, Neutral Red, known to be chemically i~~so~~nhomogeneous, was begun. A compound having the structure commonly attributed to Neutral Red was synthesized and found to have inferior staining properties. Synthesis of num~~b~~erous related phenazines and analogous to Neutral Red have shown the dependence of good staining properties on the nature and position of the substituents. The correct structure for Neutral Red is now under study.

D. Chemistry of Polysaccharides of Bacterial, Plant, and Animal Tissue Origin. Mild methods for the further purification of these substances have been worked out. The hitherto unreported presence of esterified phosphate and uronic acid components has been demonstrated by infra-red spectrography. Information regarding the type of linkage (usually 1:4) uniting the sugar units, and the steric configuration (usually α), was obtained.

E. Bioassay of New Material. With the discontinuance of screening activity of a large number of chemical agents, evaluation in our primary screen has been restricted to a relatively small number of selected materials in which we have an especial interest. More than 200 materials, of which 82 are individual compounds, 114 plant products, and others of animal origin have been bioassayed.

F. Isolation and Identification of the Tumor-Damaging Agents in *Alangium*. The activity of the bark of the Australian tree, *Alangium villosum* var. *polyosmoides*, was found to reside in the alkaloid fraction. The potent fraction has yielded at least two alkaloids active in damaging Sarcoma 37 in mice.

G. Isolation and Identification of the Tumor-Damaging Agents in *Bryonia*. Preliminary work on this isolation has been started. A potent polysaccharide has been obtained from this plant.

H. Fate and Distribution of C^{14} - tagged Colchicine in Mice. Assembly of instruments and apparatus for this work is practically complete. A paper-electrophoretic method was found best for distinguishing between trimethylcolchicinic acid methyl ether d-tartrate and iso-trimethylcolchicinic acid methyl ether d-tartrate in a mixture of the two containing at least 10γ of either one. Ultraviolet light was the best of several methods tried for detection of the spots.

NCI-251

Significance to the Program of the NCI: In the different facets of this project, new compounds have been prepared or isolated, having potency in damaging animal tumors. Many of these compounds have been prepared specifically for collaborative work with biochemists and pharmacologists. Several compounds are now under study by clinical investigators.

Proposed Course of Project: All of the facets listed in this project will be continued for the next calendar year. In addition, a new facet will be started on the preparation of new derivatives of pyridine designed to throw light on nicotinamide antagonism, 3-acetylpyridine metabolism, and the role of DPN in tumor metabolism.

10. NCI-751
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$50,465	4*	4	8*	4*	2-1/2	6-1/2*	
FY 1956	$58,372	4*	4	8*	4*	4	8*	

* Includes one Visiting Scientist

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

15. NCI-751
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. M. G. Kelly and J. L. Hartwell: J. Nat. Cancer Inst. 14, 967-1010 (1954). The Biological Effects of the Chemical Composition of Podophyllin. A Review.

2. A. W. Schrecker and J. L. Hartwell: J. Am. Chem. Soc. 76, 752-4 (1954). Components of Podophyllin. XIV. Acid-catalized Reactions of Podophyllotoxin and Its Stereoisomers.

3. A. W. Schrecker, G. Y. Greenberg, and J. L. Hartwell. J. Am. Chem. Soc. 76, 1182-1184 (1954). Components of Podophyllin. XV. Pyrolysis of Podophyllotoxin Halides.

4. A. W. Schrecker, G. Y. Greenberg and J. L. Hartwell, J. Am. Chem. Soc. 76, 1184-1185 (1954). Components of Podophyllin. XVI. Podophyllotoxin Haloacetates and Quaternary Derivatives..

5. D. L. Vivian, J. L. Hartwell and H. C. Waterman, J. Org. Chem. 19, 1136-9 (1954). Phenazine Syntheses. II. Phenazine Ethers and Phenazinols.

6. A. W. Schrecker and J. L. Hartwell, Helv. Chim. Acta, 37, 1541-3 (1954). On the Structure of Podophyllotoxin and the Peltatins.

7. J. L. Hartwell and A. W. Schrecker, J. Am. Chem. Soc. 76, 4034-5 (1954). Relationship of Anthricin, Hernandion and Cicutin to Desoxypodophyllotoxin.

8. D. L. Vivian, J. L. Hartwell and H. C. Waterman, J. Org. Chem. 19, 1641-5 (1954). Phenazine Syntheses. III. Miscellaneous Phenazines.

9. A. W. Schrecker and J. L. Hartwell, J. Am. Chem. Soc. 76, 4896-9 (1954). The Structure of Savinin.

Cont'd

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

NCI-251

16. Publications (continued)

10. A. W. Schrecker and J. L. Hartwell, J. Am. Chem. Soc. 76, (1954). Application to Tosylate Reductions and Molecular Rotations to the Stereochemistry of Lignans.

11. J. Leiter, V. Downing, J. L. Hartwell, I. Kline, A. Perrault, and M. J. Shear, Cancer Res. 15, in press (1955). Negative Data on Damage Induced in Sarcoma 37 with Diphenylethylamines.

12. A. W. Schrecker and P. B. Maury, J.A.C.S., 76, 5803 (1954). Synthesis of Nicotinic anc Isonicotinic Anhydride.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Lab. of Chemical Pharmacology
LABORATORY OR BRANCH

3. Pharmacology
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. Ncr 252
SERIAL NO

6. Pharmacologic Action of Tumor Damaging Substances on Animal and Human Malignant Cells
PROJECT TITLE

7. Morris Belkin
PRINCIPAL INVESTIGATOR(S)

8. E. Essner, H. Sato, R. Ross, D. Vivian, I. Wodinsky, I. Kline, A. Perrault, J. Leighton, J. Hartwell, M. J. Shear
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objective: Development of novel drugs, primarily from plant sources; and to study these and a variety of other tumor necrotizing compounds to determine how they bring about cell damage and cell death.

(B) Methods: The classic techniques of pharmacology, histo- and cytochemistry and tissue culture are used. New techniques are developed as necessary.

(C) Major Findings: For each of the facets of this project, the principal findings are as follows:

1. Tumor Damaging Capacity of Plant Materials

a) Four of 103 Australian poisonous plants inducdd marked damage in S37. The bark of Alangium villosum, on fractionation, has yielded two crystalline, monobasic alkaloids, one melting at 205°, the other at 238°. Studies on structure are in progress.

b) 17 plants used as drugs, fruits or vegetables, were fractionated for the presence of tumor necrotizing polysaccharides.
Active preparations were isolated from: bryony root, blood root, autumn crocus, cantaloupe, queen of the meadow, mandrake and pipe tobacco.

2. Cytochemical Studies of Cellular Damage Produced by Tumor Necrotizing Drugs.

Cells of Yoshida sarcoma and S 37, treated with podophyllotoxin and with colchicine, exhibited a significant disturbance in the content and disposition of lipid and polysaccharide which were detected as early as 6 hours after treatment,

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

and which increased during the following 24 hours.

3. Studies in Cellular Pharmacology

a) Two of 12 mouse hepatomas were successfully converted to the ascitic form. Effort is being made to correlate the histologic appearance of these tumors with their physiological behavior.

b) Cells of rat hepatoma islands have been separated with the aid of enzymes (trypsin); and the method of reformation of these islands after intraperitoneal transplantation has now been worked out.

c) The action of Nitromin (Nitrogen mustard N-oxide) on a number of ascites tumors of the mouse and rat is under investigation. The variations in susceptibility and correlation with cytologic and biologic behavior are objectives. The latency of response following drug administration and the pattern of nuclear damage are 2 interesting features to date.

4. Synthesis of Improved Vital Stains

The organic chemical aspects of this project are described in Dr. Hartwell's report. Evaluation of the vital-staining properties of these compounds is compared with that of commonly used commercial preparations of Neutral Red. Vital staining with such highly purified chemical entities is contributing to the clarification of the long-standing obscurities in this important field, and is expected to yield better vital dyes.

5. Response of Human Malignant Cells to Drugs, and the Effect of Drugs on the Invasion Properties of such Cells in Tissue Culture.

This work is prosecuted to:

a) Develop a "stable" of cultures of human neoplasms, of several histologic types, against which therapeutic agents can be evaluated for possible selective effect. Preliminary experiments have been done with acetyl podophyllotoxin-ω-pyridinium chloride (No. 3022) on cultures of HeLa.

b) Grow human malignant and normal cells in the same culture; and to control or prevent the destructive invasion of the normal cells by the malignant cells thru the use of chemical agents.

(D) Proposed Course of Project:

The various facets of this project will be continued with particular stress on obtaining information as to how a tumor necrotizing compound brings about cellular damage. Such information is greatly needed in our effort to develop newer and better drugs with which clinical chemotherapy can be successfully accomplished.

10. NCI-252
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$62,421	5*	3	8*	5*	3	8*	
FY 1956	$62,329	5*	3	8*	5*	3	8*	

* Includes one Visiting Scientist.

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Laboratory of Pathology, NCI.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No

15. NCI-752
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. Experiments on an Ascites Hepatoma. I. Enzymatic Digestion and Alkaline Degradation of the Cementing Substances and Separation of Cells in Tumor Islands. by E. Essner, H. Sato, and M. Belkin, Experimental Cell Research 7: 430-437, 1954.

2. II. Intraperitoneal Transplantation of Free Tumor Cells Separated from Islands of the Rat Ascites Hepatoma. by H. Sato, E. Essner, and M. Belkin. Experimental Cell Research (in press)

3. Separation and Retransplantation of Free Tumor Cells from Islands of the Rat Ascites Hepatoma. by H. Sato, E. Essner and M. Belkin. Gann 45: 563-66, 1954.

4. Intraperitoneal Transplantation of the Yoshida Ascites Sarcoma and the Ascites Hepatoma to Various American Strains of Rats. by H. Sato. Journal National Cancer Institute (in press)

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Lab. of Chemical Pharmacology
LABORATORY OR BRANCH

3. Pharmacology
SECTION OR SERVICE

4. .
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-253
SERIAL NO

6. Studies of Host-Tumor Relationship in Tumor Chemotherapy
PROJECT TITLE

7. A. Goldin
PRINCIPAL INVESTIGATOR(S)

8. S. Humphreys, J. Venditti, and Prof. N. Kaplan (Johns Hopkins)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives

A. 1. To study the mode of action of metabolic antagonists with respect to host and tumor.

2. The establishment and employment of therapeutic principles and procedures in the management of tumor growth in animals.

Methods

B. Macrobiological assay procedures under continuing development for animals with and without tumor.

Major Findings

C. 1. Comparison of drug-effectiveness. Amethopterin was more effective than aminopterin on any one of a number of treatment schedules in increasing the survival time of leukemic mice.

2. Development of assay procedures. A macrobiological assay procedure was developed, which takes into account the toxicity of drugs for the host, to determine whether anti-tumor synergism is obtained on combination drug therapy. In a model experiment, anti-leukemic synergism was not observed on treatment with amethopterin plus 6-mercaptopurine.

3. Metabolites and antimetabolites. Protection was afforded against the lethal toxicity of 6-mercaptopurine in mice by the administration of purine ribosides and ribotides and diphosphopyridine nucleotide. These metabolites also blocked the anti-leukemic effectiveness of 6-mercaptopurine. 3-acetyl

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

pyridine toxicity for mice is blocked by nicotinamide or diphosphopyridine nucleotide.

Diphosphopyridine nucleotide provides provides protection against the combination of an ordinarily lethal dose of 6-mercaptopurine plus an ordinarily lethal dose of 3-acetyl pyridine. Nictotinamide also inhibits the formation of the 3-acetyl pyridine analog of diphosphopyridine nucleotide in mouse brain homogenates. Injection of 3-acetyl pyridine into mice with tumor results in the formation of the acetyl pyridine analog of diphosphopyridine nucleotide in the tumor tissues. The analog has been isolated from tumor tissue and identified. Several of the antitubercular agents including isonicotinic acid hydrazide and Marsilid also form analogs with diphosphopyridine nucleotide. These drugs, as well as 3-acetyl pyridine, potentiate ~~and~~ the anesthetic action of nembutal.

4. Management of animal tumor. In a series of experiments employing appropriate treatment schedules of 6-mercaptopurine, aminopterin or amethopterin, and employing delayed administration of citrovorum factor with the "antifolics", leukemic mice were kept alive for extended periods of time, and a low but consistent percentage of the mice did not die. In one experiment, on extended multiple treatment with amethopterin, and amethopterin plus delayed citrovorum factor, all of the untreated leukemic mice succumbed in 10-12 days following tumor implantation, while over 50% of the treated mice were alive after 65 days. In this experiment 5 out of 40 mice are still alive and show no evidence of tumor 150 days following tumor implantation. The possibility that "total regressions" observed in these experiments are attributable to host resistance has been ruled out. In this experiment each mouse was treated on a prescribed regimen subject to modification based on the animal's response to treatment.

D. Significance to program of Institute and proposed course of project.

The experiments reported here are designed to provide basic information pertaining to host-tumor relationships in chemotherapy and to establish principles for treatment in animals which may be of use in application to clinical chemotherapy. The various phases of this program will be continued and broadened during the next year. Much of the work on metabolites and anti metabolites was accomplished in a collaborative continuing program with Dr. N. O. Kaplan's group of the McCollum Pratt Institute of the Johns Hopkins University, Baltimore, Md.

PROJECT REPORT FORM (Cont'd)

10. NCI-753
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 40,921	1	6	7	1	6	7	
FY 1956	$ 41,183	1	6	7	1	6	7	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Collaboration with Dr. N. O. Kaplan of the McCollum-Pratt Institute, Johns Hopkins University. Funds, facilities and staff have been provided by him in joint program.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

15. NCI-253
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. Effect of delayed administration of citrovorum on the anti-leukemic effectiveness of aminopterin in mice. A. Goldin, N. Mantel, S. W. Greenhouse, J. M. Venditti and S. R. Humphreys. Cancer Research 14, 43-48, 1954.

2. Demonstration of protection against the lethal toxicity of 6-mercaptopurine in mice. A. Goldin. J. Nat. Cancer Inst. 14, 1247-1252, 1954.

3. Factors influencing the specificity of action of an antileukemic agent (Aminopterin). Time of treatment and dosage schedule. A. Goldin, N. Mantel, S. W. Greenhouse, J. M. Venditti and S. R. Humphreys. Cancer Research 14, 311-314, 1954.

4. Significance of enzymatically catalyzed exchange reactions in chemotherapy. N. O. Kaplan, A. Goldin, S. R. Humphreys, M. M. Ciotti and J. M. Venditti. Science 120, 437-440, 1954. (Joint publication with McCollum Pratt Institute of the Johns Hopkins University)

5. Studies on the toxicity and anti-leukemic action of 6-mercaptopurine in mice. A. Goldin, J. M. Venditti, S. R. Humphreys, D. Dennis, N. Mantel, and S. W. Greenhouse. Annals N. Y. Acad. Sci. 60, Article 2, 1954.

6. Factors influencing the specificity of action of an antileukemic agent (Aminopterin). Multiple treatment schedules plus delayed administration of citrovorum factor. A. Goldin, J. M. Venditti, S. R. Humphreys, D. Dennis, N. Mantel, and S. W. Greenhouse. Cancer Research (in press).

7. A quantitative comparison of the anti-leukemic effectiveness of two folic acid antagonists. A. Goldin, J. M. Venditti, S. R. Humphreys, D. Dennis, N. Mantel and S. W. Greenhouse. J. Nat. Cancer Inst. (in press).

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

A. Goldin--Received appointment as Research Associate in the McCollum-Pratt Institute of the Johns Hopkins University, Balt. July 1, 1954.

A. Goldin--Invited to talk and participate at Conference on "6-mercaptopurine" held at the New York Academy of Sciences, April 30 and May 1, 1954. Title of paper presented "Studies on the Toxicity and Antileukemic Activity of 6-Mercaptopurine in Mice."

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Lab. of Chemical Pharmacology
LABORATORY OR BRANCH

3. Biochemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-254
SERIAL NO

6. Effect of tumor-damaging agents on the biochemical and physiologic properties of normal and malignant tissues.
PROJECT TITLE

7. J. Leiter
PRINCIPAL INVESTIGATOR(S)

8. V. Waravdekar, M. Kelly, D. Fitzgerald and M. Freeman
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

(A) Objectives

To elucidate the mechanism of action of tumor-damaging drugs by determining the biochemical changes they produce in tumors.

(B) Methods Employed

1. Determination of enzyme and other biochemical activities in normal and malignant tissues from hosts treated with tumor-damaging agents.

2. Separation of cellular components of normal and malignant cells to localize the intracellular site of action of these agents.

3. Step-wise enzymatic degradation of tumor-damaging polysaccharides.

4. Modification of the production of the Shwartzman phenomenon with polysaccharides to illuminate the relationship to tumor-damaging effects.

(C) Major Findings

1. Tumor tissue from animals injected with alpha-peltatin showed a diminished glucose utilization as reflected in anaerobic glycolysis. This effect appeared to be related to a marked diminution in endogenous diphosphopyridine nucleotide (DPN) in the tissue. Fortification of the substrate medium with a large excess of DPN restored the ability of treated tumors to glycolyze.

2. The relationship of the enzymatic changes produced by these drugs to those produced by physical disruption of intracellular components was studied. Mechanical disruption of mitochondria reduced cytochrome oxidase activity and succinoxidase activity in a fashion similar to drug treatment. On the other hand,

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-254

enzymes such as uricase or glutamic dehydrogenase, which are unaffected or markedly increased by mechanical disruption of mitochondria, were markedly decreased following injection of tumor-damaging compounds. Adenosine deaminase and nucleoside phosphorylase, enzymes found in the soluble portion of the cell, were unaffected after injection of tumor-damaging agents.

3. Malic oxidase, but not malic dehydrogenase, activity in tumor tissue was markedly affected following treatment with such drugs. This parallels previous findings with succinoxidase and succinic dehydrogenase activity. Other related enzymes, such as malic-cytochrome c reductase, DPN-cytochrome c reductase and $DPNH_2$ oxidase, were also markedly reduced.

4. Fractionation of homogenates of hepatoma, from untreated animals and from animals previously injected with a soluble derivative of podophyllotoxin, into nuclear, mitochondrial and supernatant fractions revealed a small decrease in the desoxyribosenucleic acid (DNA) of the nuclear fraction and a corresponding increase in the supernatant fraction. Overall cytochrome oxidase activity in treated tumors was reduced to 15 percent of that in the controls, but this residual activity was largely concentrated in the mitochondrial fraction, as in the controls. Only about 2/3 of the ribosenucleic acid (RNA) found in untreated tumors was present in tumors from treated animals; the principal loss in RNA was in the supernatant fraction. These was no change in total nitrogen in the homogenates, and the distribution of N in each cellular fraction was the same in both treated and untreated tumors.

5. A microbiological method specific for measuring thymidine levels in serum, normal and malignant tissues was developed. Experiments are under way to determine the changes in thymidine levels produced by tumor-damaging agents.

6. Further attempts to hydrolyze P-25 with various enzymes from vegetable sources or from microorganisms produced no significant release of reducing sugars. Heating P-35 in buffered solutions at 100° C for 30 minutes produced no loss in tumor-damaging potency or in lethal toxicity.

(D) Significance

These studies are designed to obtain basic biochemical information on cellular metabolism of tumors and normal tissues as affected by administration of tumor-damaging drugs. This information may provide insight into the nature of the damage produced and also lead to an understanding of the differences between normal and malignant tissues. Experiments with the Shwartzman reaction are designed to yield information on the relationship of local vascular responses in sensitized tissues to polysaccharides, and their mechanism producing hemorrhagic necrosis in tumors.

NCI-254

(E) Proposed Course of Project

The work described under 9(C) will be extended. The relationship of the changes in the oxidase activities to intermediate components of the cytochrome system (Slater factor and cytochrome b_5) will be explored. The effects produced by these drugs on nucleoprotein metabolism and on the role of DPN in the metabolism of tumor tissue will be further investigated.

PROJECT REPORT FORM (Cont'd)

10. NCI-754
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 51,068	3-1/2*	3-1/2	7 *	3-1/2*	3-1/2	7*	
FY 1956	$51,076	3-1/2*	3-1/2	7*	3-1/2*	3-1/2	7*	

*Includes 1 Visiting Scientist.

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

15. NCI-754
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. Waravdekar, V. S., Paradis, A. D. and Leiter, J.: Enzyme Changes Induced in Normal and Malignant Tissues with Chemical Agents. IV. Effect of Alpha-peltatin on Glucose Utilization by Sarcoma 37. J. Nat. Cancer Inst. (in press)

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Lab. of Chemical Pharmacology
LABORATORY OR BRANCH

3. Biochemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5 NCI-755
SERIAL NO

6. Development of Drugs for Clinical Investigation
PROJECT TITLE

7. J. Leiter
PRINCIPAL INVESTIGATOR(S)

8. M. Kelly, D. Fitzgerald, V. Waravdekar, J. Hartwell, D. Rall, A Perrault, M. J. Shear
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives:

1. To develop chemical agents capable of influencing tumors in experimental animals and to study the relationship of their chemical structure to biological activity.

(B) Methods Employed

Production of damage in tumors following a single subcutaneous injection of chemical agents into mice bearing a variety of transplanted tumors; the determination of the range between the maximum tolerated dose (MTD) and minimum effective dose (MED) (therapeutic index) for a single injection; acute and chronic toxicity in normal animals (mice, rats, dogs); optimum vehicle and route of administration; etc.

(C) Major Findings

1. About 80 new compounds were screened against Sarcoma 37 by our usual technique. Included were: additional N-substituted derivatives of colchicine (related to demecolcin); naturally occurring glucosides of podophyllotoxin as well as synthetic soluble derivatives; furoic acid derivatives (inhibitors of glutamic dehydrogenase); and α,β-unsaturated lactones and ketones. Several compounds of all these types of compounds were found active in damaging Sarcoma 37. All the N-substituted colchicine derivatives related to demecolcin had high potency. Correlation between the rate of hydrolysis of the water-soluble derivatives of podophyllotoxin and biological activity was obtained. For example, acetylpodophyllotoxin-ω-pyridinium chloride, a high potent compound, hydrolyzed

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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rapidly (50%) within 30 minutes to yield the active parent substance podophyllotoxin. Those derivatives hydrolyzing at a slower rate were less active.

2. A survey of tumor-damaging extracts of coniferous evergreens was completed. Although most of the active plants were in a narrow group of taxonomically related genera (Juniperus and Libocedrus), one each from species of Podocarpus and of Pilgerodendron was active. Silicicolin, the active component, was isolated from a species of Chamaecyparis and of Libocedrus.

3. Because of the potency of bulbs of the family Amaryllidaceae against malaria parasites, a brief survey of their potency against animal tumors was made. Of some 70 varieties examined, extracts from about 10 percent of these produced damage in Sarcoma 37; these included species of Polianthes, Lycoris and Narcissus. A methanol and acetone extract of narcissus bulbs yielded a fraction with about 15 times the potency of the original bulb and with comparatively low toxicity. A few alkaloids from Amaryllidaceae (obtained from the plant program of the Heart Institute) were active against tumors, but their potency was not as great as some of the crude extracts, nor could their activity account for the total activity of the bulbs.

4. Twelve polysaccharide preparations from Pneumococcus and one from B. typhosus (obtained from Squibb and Co.) were examined for tumor-damaging potency. This typhoid polysaccharide (a pyrogen) was potent and had a ratio MTD/MED of 8. Three pneumococcus preparations had similar ratios of 8, 4 and 2. A starch-like material from Bryonia Root, which was active against Sarcoma 37, was digested with amylase. About 90 percent of the material was converted to glucose and maltose. The non-dialyzable residue had about 10 times the potency of the original product.

5. Acute and chronic toxicity studies of 2 colchicine derivatives were carried out in mice, rabbits and dogs to implement a joint research program with the Clinical Branch of the NCI. Preparations of alpha-peltatin for patient use were made and preliminary testing for toxic action in experimental animals performed, prior to their use in a patient by the Surgical Service. A selected group of podophyllotoxin and colchicine derivatives were made available to the clinical staff (Dr. Sullivan) for evaluation on human tumors by Dr. Sullivan's intratumoral techniques.

6. Some pharmacologic effects of two related classes of tumor-damaging compounds (phenazines and quinoxalines) were studied. Total body tremors similar to tonic convulsions, and clonic convulsions, were toxic symptoms produced with some phenazine compounds. Some closely related quinoxaline compounds did not give rise to these symptoms. It was possible to correlate substituents on various parts of the phenazine molecule with this toxic phenomenon.

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(D) Significance to Cancer Research

Development of new drugs for investigations in clinical chemotherapy.

(E) Proposed Course of Project

Emphasis will be placed on the working up of active compounds for investigation on a clinical level. This aspect has been actively initiated during the past few months in close conjunction with the Clinical Director and his staff, and will be more extensively pursued during the next year.

PROJECT REPORT FORM (Cont'd)

10. NCI-255
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 21,886	1-1/2	1-1/2	3	1-1/2	1-1/2	3	
FY 1956	$ 21,890	1-1/2	1-1/2	3	1-1/2	1-1/2	3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

NONE

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

15. NCI-255
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. Kelly, M. G. and Hartwell, J. L.: The Biological effects and the Chemical Composition of Podophyllotoxin. A Review. J. Nat. Cancer Inst. 14: 967-1010 (1954).

2. Leiter, J., Perrault, A., Hartwell, J. L., Kline, I. and Shear, M. J.: Negative Results with Diphenylethylamines in Producing Damage in Sarcoma 37. Cancer Research, Supplement No. 2 (in press).

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-300
SERIAL NO

6. Polycysteine Peptides and Proteins
PROJECT TITLE

7. Greenstein, Winitz, Otey, Izumiya (visiting scientist), Wade (visiting scientist)
PRINCIPAL INVESTIGATOR(S)

8. ----------
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The objectives of this project are: (a) to prepare by organic chemical synthesis peptides containing two or more cysteine residues, (b) to oxidize such peptides by controlled procedures to the corresponding disulfide forms, (c) to ascertain by physical and other procedures the polymeric configurations and sizes of these disulfide forms, and (d) to subject such polymeric compounds to enzymatic studies in vitro and to physiological studies in vivo. Simultaneous studies are conducted on pure proteins with several cysteine residues to see what products result from controlled oxidation as revealed by enzymatic and physical criteria.

The major findings of this project during the past year are the following. The oxidation of L-cysteinyl-L-cysteine at pH 6.5 leads to a completely different L-cystinyl-L-cystine than that obtained by oxidation at pH 8.5, whereas the same oxidation of L-cysteinyl-D-cysteine or D-cysteinyl-L-cysteine leads to a disulfide product whose formation is the same whether at pH 6.5 or pH 8.5. The infra-red and ultraviolet absorption spectra are the same for the L-cystinyl-L-cystine prepared at pH 6.5 or pH 8.5, but their titration curves differ, their optical rotations are considerably different, as are their R_f values.

Future studies on this project envisage (a) the preparation of still larger synthetic polypeptides in which the SH groups are

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-300

Continuation Sheet

separated by amino acids of different optical configuration, (b) the preparation of synthetic polypeptides containing at least three cysteine residues, and (c) investigation of such enzyme proteins as myosin which contain several free SH groups capable of oxidation to new proteins linked by disulfide residues and with perhaps new enzymatic and physical properties.

The significance of this project to cancer research lies in the fact that intracellular proteins are invariably characterized by the possession of free SH groups on their surface, and the conversion of such proteins into disulfide forms will be dependent on the oxygen tension available to the tissue in which such proteins occur. The reverse of this oxidation is most probably accomplished by glutathione. This type of reversible SH-SS equilibria involving proteins must be different in cancer tissues which possess a more anaerobic state, and information developed by investigations such as these will illuminate the chemical state of proteins in tissues under different conditions of oxidation. This approach has not hitherto been studied anywhere, and is novel to this project.

PROJECT REPORT FORM (Cont'd)

10. M-1-300
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 15,514	3	---	3	1-2/3	---	1-2/3	
FY 1956	$ 15,458	3	---	3	1-2/3	---	1-2/3	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-300
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

N. Izumiya and J. P. Greenstein, Studies on Polycysteine Peptides and Proteins. I. Isomeric Cystinylcystine Peptides. Archiv. Biochem. and Biophys., 52, 203 (1954).

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Office of the Chief
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-301
SERIAL NO.

6. Secretarial Duties in the Laboratory of Biochemistry
PROJECT TITLE

7. B. A. Gantz, C. Cissel, A. Sigwald, and V. Patkus
PRINCIPAL INVESTIGATOR(S)

8. ---------
OTHER INVESTIGATORS

PROJECT DESCRIPTION

The objectives of the Secretarial Unit in the Office of the Chief are to: Maintain personnel, correspondence, reprint, and requisition files, keep an accurate and current record of Laboratory expenditures, calculate and record leave and overtime, maintain a Laboratory library, type manuscripts, letters, memoranda, lantern slides, requisitions, shop orders, and miscellaneous articles and charts. The above duties are performed for 26 professional employees and for 37 subprofessional employees.

Since January 1954, this Unit has typed the following: Approx. 2,110 original pages of manuscripts, approx. 1,136 letters and memoranda, approx. 51 lantern slides, approx. 550 pages of miscellaneous material, approx. 1,186 requisitions (both stock and other objects), approx. 197 Cancer Instrument Shop orders, approx. 122 NIH Instrument Section orders, approx. 188 Maintenance Work Requests, approx. 151 Requests for Services, approx. 65 Reports of Surplus Property, approx. 51 Shipment Requests, and approx. 35 Requests for Animals.

In the future this Unit will continue to do its utmost to produce as much work as possible and to perform this work accurately and rapidly.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. 151-301
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$21,064	---	4	4	---	4	4	
FY 1956	$21,272	---	4	4	---	4	4	

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2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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3. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. LCI-301
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Miss Betty Ann Gantz awarded Superior Accomplishment Award on November 10, 1954, by Dr. J. R. Heller, Director, NCI.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Office of the Chief
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. A21-302
SERIAL NO.

6. Analytical Unit
PROJECT TITLE

7. Robert Koegel, James Williams, Rita McCallum, Eleanor Thompson
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The Analytical Section of the Biochemistry Laboratory operates on a research and service level. Its research function is to collaborate with the independent investigators of the laboratory in the application of the most recent developments in analytical chemistry to their specific problems; the section in this fashion becomes a part of the research program of the entire Biochemistry Laboratory.

On a service level the analytical section makes available on a routine basis the following procedures:

1. Microchemical analysis for C, H, N, S the halides; functional group analysis for ethoxy, methoxy, acetyl etc.
2. Ultra microchemical techniques particularly for phosphorous, iron, and halides in the 100.0μg range to 1.0μg.
3. Flame photometric techniques for Na, K^+, Ca^{++} and Mg^{++}.
4. Karl Frscher procedure for absolute estimation of H_2O in organic samples.
5. Spectrophotometric analysis using the Cary spectrophotometer for the visible and ultraviolet regions and the Perkin-Elmer spectraphotometer for the infrared region.

Major Findings:

1. Utilizing the Perkin-Elmer model no. 21 recording spectrophotometer and the recently developed potassium bromide pellet technique, the infrared spectra of several enatiomorphic and diastereoisomeric pairs of amino acids were studied. This study demonstrated conclusively that the infrared spectra of enantiomorphic pairs are identical, that the spectra of members of a diastereoisomeric pair are different and that these differences permit an assignment of the spatial orientation of the functional groups . Specifically

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-302

Continuation Sheet

it was possible to assign the cis configuration to allohydroxy proline and the allo form of α aminotricarballylic acid.

2. Utilizing infrared spectrophometric techniques, it was specifically demonstrated that the failure of a group of compounds similar to α Keto glutaramate to exhibit the chemical properties of an α Keto group was due to hydrogen bonding involving the oxygen of the α Keto carbonyl.

3. The file of ultraviolet, visible and infrared spectra of all compounds synthesized and isolated by members of the biochemistry laboratory — and in particular the optically and chemically pure amino acids, peptides and polypeptides synthesized here for the first time — is being constantly enlarged. The spectra of these compounds are a physical characteristic, as specific as their melting points and may be used both for unequivocal identification and quantitative estimation.

4. The efficiency of the section is indicated by the fact that the time of the one professional member has, during 1954, been devoted exclusively to infrared and ultraviolet spectrophotometric problems. The service function of the section amounting to 1,400 samples, 5,000 individual tests has been most efficiently performed by three non-professionals, a GS7, GS6, and GS3.

Significance to Cancer Research:

1. The file of ultraviolet, visible and infrared spectra being compiled in this section will find application in the qualitative identification and quantitative estimation of metabolites isolated in studies on various carcinogens.

2. The Karl-Fischer technique for the absolute determination of H_2O in organic material-which has been established as a routine analysis-is to be employed in characterization of haemoglobin fractions.

3. The American Instrument Company of Silver Spring, has placed in routine production glassware for micro Kjeldahl digestion and distillation developed in conjunction with this section.

Objectives for 1954:

1. Study the solid state infrared spectra of the amino acids, peptides and polypeptides synthesized and isolated by members of the biochemistry laboratory. This examination is tobe extended into the far infrared region specifically from 15.0μ to 40.0μ.
It is felt that the spectra of these model compounds which are chemically and optically pure will permit a more intelligent interpretation of the infrared spectra of highly purified protein molecules and protein fractions.

2. To follow protein fractionation procedures with infrared spectra hoping to correlate a specific absorption band with increased purity of the protein or enzyme, as demonstrated by other techniques of assay.

3. To examine in H_2O, their natural environment, the infrared spectra of the amino acids, peptides and polypeptides synthesized and isolated by members of this laboratory.

4. To develop quantitative techniques using infrared spectra, for estimating the amount of cis and transisomers, or the normal and allo forms in a mixture of diastereoisomers.

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Continuation Sheet

5. To reexamine the extinction coefficient of the peptide bond in the Schuman region using the model amino acids, peptides, dehydropeptides, and polypeptides synthesized, optically and chemically pure, by members of the biochemistry laboratory. With this extinction coefficient accurately established, utilize it to develop methods for estimating peptidase activity.

6. Continue the service function of the section on the same level of efficiency as established in previous years.

PROJECT REPORT FORM (Cont'd)

10. NCI-302
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$25,125	1	3	4	1	3	4	0
FY 1956	$25,220	1	3	4	1	3	4	0

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12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for 14, 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-303
SERIAL NO

6. Intracellular peptidases
PROJECT TITLE

7. Drs. S. M. Birnbaum, M. Winitz, J. P. Greenstein. and S.-C. J. Fu
PRINCIPAL INVESTIGATOR(S)

8. Betty Whitaker
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this study are threefold:

1. To survey the various enzymes by which the tissues handle proteins and their derivatives such as peptides and amino acids.
2. To elucidate the mechanisms by which these enzymes accomplish their function.
3. To study the ways in which the tumor differs from the normal tissue with respect to these systems.

Methods employed:

The development of procedures for the preparation of optically pure amino acids has supplied the starting materials for the synthesis of a wide variety of enzymatically susceptible derivatives. Treatment of these derivatives e.g., peptides, amino acid esters etc. with various buffer-homogenate systems yields hydrolytic products in varying amounts dependent upon their relative susceptibility. The various enzymes responsible for these hydrolyses are then further defined by fractionation or partial denaturation studies. Similar studies applied to cancer tissue give fundamental information as to the differences in enzyme patterns accompanying the neoplastic transformation.

The effect of systematic modification of the substrate on its susceptibility to the action of purified enzymes yields information on the intimate nature of the enzyme substrate relations.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-303

Continuation sheet

Major findings:

The hydrolysis of corresponding L and D amino acid esters by tissue homogenates and purified fractions thereof has been studied in some detail. As yet no definite pattern has emerged, both enantiomorphs being highly susceptible. It is tentatively concluded that most of the activity against amino acid esters is due to a non-specific esterase.

The effect of the optical configuration of the acyl group on two carboxy peptidases, acylase I and pancreatic carboxypeptidase, was studied. In all cases the L acyl L amino acid was most susceptible. The difference between the L and D acyl L amino acids was relatively small, however, except in the case of true dipeptides for acylase I and of carbobenzoxy-dipeptides for pancreatic carboxypeptidase. Additional centers of enzyme contact were postulated to explain these observations.

Significance to cancer research:

An understanding of the ways in which the normal tissue handles the building stones of the tissue proteins and of the ways in which the tumor differs from the normal is fundamental to an understanding of the general problems of growth and cancer development.

Proposed course of project:

Further efforts will be made to characterize the enzymes responsible for hydrolysis of the labile amino acid esters and amides. Similar enzymes will be sought in tumor tissue and their relative levels and specificities compared. Further work on the dehydropeptidases is also contemplated.

PROJECT REPORT FORM (Cont'd)

10. NCI-303
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 20,465	5	1	6	2	1/3	2-1/3	
FY 1956	$ 14,140	4	1	5	1-1/3	1/3	1-2/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

15. NCI-303
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

(1) Fu, S. C. J., Birnbau, S. M., and Greenstein, J. P.
Influence of Optically active Acyl Groups on the Enzymatic Hydrolysis of N-Acylated-L-amino acids.
J.A.C.S. 76, 6054, 1954.

(2) Birnbaum, S. M. and J. P. Greenstein
Peptidases in Renal and Hepatic Tissues.
Bulletin of the Research Council of Israel IV, 6 (1954).

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-304
SERIAL NO

6. Possible carcinogenic and anticarcinogenic properties of L and D amino acid combinations with carcinogenic amines.
PROJECT TITLE

7. Birnbaum, Winitz, Greenstein
PRINCIPAL INVESTIGATOR(S)

8. Brooks, Whitaker
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Project:
Possible carcinogenic and antiocarcinogenic properties of L and D amino acid combinations with carcinogenic amines.

Objectives:
The ability of various tissues to hydrolyze these carcinogen derivatives will be correlated with the tissue susceptibility to carcinogenesis. Possible anti carcinogenic properties will be sought among the inactivated carcinogens.

Methods Employed:
Some fifty different amino acid derivatives of carcinogenic amines have been synthesized in highly purified form. These include combinations of various optically pure L and D natural and synthetic amino acids with three different non tissue specific carcinogens; aminofluorene, aminobiphenyl and benzidine. The hydrolytic susceptibility of all of these compounds to various rat tissue homogenates will be determined by a combination of colorimetric and ninhydrin-CO_2 procedures. Certain of these compounds, which show interesting enzymatic susceptibilities, will then be tested for carcinogenic activity in the rat. The occurence and nature of any tumors formed will be observed and a relation between tissue susceptibility and the ability of that tissue to form the free carcinogen enzymatically will be sought. Inactive derivatives will be tested for specific anticarcinogenesis by injection with a corresponding active carcinogen, and for non specific anticarcinogenesis by inhibition of the growth of standard tumor transplants.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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Continuation Sheet

Major findings:
The successful synthesis of most of the proposed amino acid derivatives has been accomplished. Tissue studies so far indicate with one or two possible exceptions a high degree of optical specificity of the enzymes involved but with a wide range of relative susceptibility of the various L amino acid derivatives.

Significance to Cancer Research:
The direction of a non tissue specific carcinogen to a given target tissue as well as the discovery of structural anticarcinogenic compounds may prove to be an important tool in the study of the mechanism of carcinogenesis.

Proposed course of project:
The project as outlined should be completed within the next calendar year. Further work will develop from any interesting relations uncovered.

PROJECT REPORT FORM (Cont'd)

10. M-1-304
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$16,620	5	1	6	1-1/2	1/2	2	0
FY 1956	0	0	0	0	0	0	0	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Sec.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-305
SERIAL NO

6. Polarimetric criteria for amino acids and peptides
PROJECT TITLE

7. Miles C. Otey, Dr. J. P. Greenstein, Dr. S. M. Birnbaum, and Dr. M. Winitz
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Objectives:
To investigate the value of optical rotatory power as a means of characterizing amino acids and peptides as to optical configuration.

Methods Employed:
(a) Optical rotation is measured at six wavelengths in the visible and near u.v. portions of the spectrum. The resulting rotatory dispersion is then analyzed to ascertain the optical configuration of the compound. (b) Rotations of a given compound are taken in aqueous solution and in acid solution, and the configuration may be determined with the aid of the Lutz-Jirgensons rule.

Major Findings: The rotatory dispersions of aqueous and acid solutions of 42 amino acids (of known configuration) have been recorded and analyzed. In all cases, analyses have led to the correct configuration. It has also been possible to determine the configuration about the α-carbon atom of amino acids with more than one asymmetric center.

Significance to Cancer Research:
Amino acids and peptides are intimately related to the metabolism of proteins. As a result they are studied in many cancer research programs. It is quite important to have a simple, fast and reliable means of characterizing these substances with respect to their optical configuration.

Proposed Course of Project:
These techniques have been incorporated into the program as regular procedures, and will be applied to new compounds with which investigators in this laboratory must work.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. AC1-305
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 13,987	4	0	4	1-1/2	0	1-1/2	
FY 1956	$ 3,092	1	0	1	1/3	0	1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

No entries for 15, 16, 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-306
SERIAL NO

6. The large scale resolution of amino acids
PROJECT TITLE

7. Winitz. Birnbaum and Greenstein
PRINCIPAL INVESTIGATOR(S)

8. - - - -
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:

The objective of this project is to so modify and extend the enzymic resolution procedures developed in this Laboratory as to permit the ready accessibility, in the laboratory, of the optically pure D- and L- forms of a variety of amino acids in pilot plant quantities.

Methods employed:

A suitable acyl or amide derivative of a DL-amino acid is subjected to the hydrolytic action of an appropriate peptidase (hog kidney amidase, acylase I or acylase II). Since only the L-amino acid derivative is susceptible to enzymically catalyzed hydrolytic action, the liberated L-amino acid may be separated from the highly resistant D-amino acid derivative by differential solubility. Isolation of the D-amino acid becomes permissible through acid hydrolysis of its precursor derivative. Amino acids so obtained have a minimum optical purity of 99.9%.

Major findings:

Studies in this Laboratory on the separation and characterization of intracellular peptidase systems of normal and neoplastic tissues have required that large stocks of optically pure amino acids for the synthesis of appropriate substrates be readily accessible. This need was met through the development of simple, convenient and rapid enzymatic resolution methods for the preparation of highly pure L- and D- forms of amino acids. During the past five years, these methods not only have been used for the resolution of some fifty amino acids in this Laboratory alone, but have, in several instances, been adopted commercially. This has resulted in both lower cost and greater availibility of optically pure amino acids to a large number of

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-306

Continuation sheet

research laboratories.

Significance to cancer research:

In order to study the specificity of various enzyme systems (L- and D- amino acid oxidases, peptidases) of normal and neoplastic tissues, amino acids and derivatives thereof, in a very high degree of optical purity, become a necessary prerequisite. Such compounds, in quantity, are also needed to study any differences that might exist in the nutritional requirements of normal and tumor bearing animals.

Proposed course of project:

For the enactment of several of the major programs of this Laboratory, the production of optically pure amino acids in pilot plant quantities is now underway. Commercial procurement of these compounds is unsatisfactory for two reasons. First, these compounds, where available, cannot be obtained in the desired degree of purity and, secondly, the cost of these compounds would be prohibitive. Based on the lowest current commercial prices, it is estimated that some $4,000,000 worth of optically active amino acids will be produced within the next year at only a fraction of the cost (less than $100,000) in terms of time, material and personnel.

PROJECT REPORT FORM (Cont'd)

10. AC1-306
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 22,490	3	3	6	1	2-1/2	3-1/2	
FY 1956	$ 25,229	3	3	6	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13 COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

5. Lel-306
SERIAL NO.

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6. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

none

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Dr. Jesse P. Greenstein given Distinguished Service Award of the Department of Health, Education and Welfare by Secretary Hobby in April 1954.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-307
SERIAL NO

6. Diastereomeric α-amino acids and corresponding α-hydroxy acids
PROJECT TITLE

7. Winitz, Greenstein and Birnbaum
PRINCIPAL INVESTIGATOR(S)

8. Inglett, Izumiya, Koegel and Otey
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
The objective of this project is to investigate the structural relationship between those amino acids and corresponding α-hydroxy acids with more than a single center of asymmetry and their physical, chemical and biological behavior.

Methods employed:
The various methods employed include physical (optical rotation, rotatory dispersion, X-ray diffraction, infra-red spectroscopy), chemical (synthesis and resolution of diastereomeric amino acids as well as their nitrous acid deamination to the corresponding α-hydroxy acids) and biological (rates of peptidase and oxidase action on appropriate substrates) procedures.

Major findings:
The synthesis and resolution of α-aminotricarballylic acid to the four optically pure stereoisomers as well as their nitrous acid deamination to the corresponding isocitric acid lactones has been effected. Use of the latter compounds as substrates in the isocitric acid dehydrogenase – triphosphopyridine nucleotide system showed that only the stereoisomer which corresponded to natural isocitric acid showed any demonstrable activity. (Greenstein, Izumiya, Winitz and Birnbaum).

The contribution (partial molar rotation) of the α- and ω-asymmetric centers to the observed molar rotations of several diasymmetric amino acids in water, 5 N hydrochloric acid and glacial acetic acid was calculated. These calculations demonstrated that the negative shift in optical rotation exhibited by the addition of acid to an aqueous solution of threo-L-β-phenylserine,

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-307

Continuation Sheet

which was contrary to the empirical rule of Lutz and Jirgensons, was attributable to the very marked negative shift of the partial rotation of its -asymmetric carbon stom. This served to completely mask the lesser shift of the partial rotation of the α-asymmetric center in the positive direction. Calculation of the partial molar rotation of the α- and -asymmetric carbon atoms of four other diasymmetric L - amino acids, as well as their L - allo isomers showed a similar water-to-acid shift in the partial rotations of their α-asymmetric centers. The specific application of this rule to the partial rotation of the α-asymmetric center served to clarify it with respect to α-amino acids with more than one center of asymmetry. On the basis of structural considerations, the rule was also clarified with regard to L-isovaline (which show a negative water to HCl shift in optical rotation) to include only amino acids bearing a hydrogen atom on the α-asymmetric center. Since this modified rule shows no known exceptions for some fifty amino acids tested, the partial molar rotation data in water and hydrochloric acid was used for the assignment of configurations to the four optical isomer of α-amino-tricarballylic acid, as well as to the four corresponding isocitric acids which follows therefrom. (Winitz, Birnbaum, and Greenstein).

By virtue of the greater susceptibility of L-acyl-L-amino acids over D-acyl-L-amino acids to the action of renal acylase I, a method of determining the optical configuration of the β-asymmetric center of isoleucine has been developed. For this purpose, dl-α-methylbutyryl-L-norleucine was subjected to the action of the enzyme, yielding as a hydrolytic product a mixture of free (+) and (-) α-methylbutyric acids in which the former predominated. Since (+)-α-methylbutyric acid is derivable from L-isoleucine (and D-alloisoleucine), the β-asymmetric center of these stereomers has been assigned the L-configuration. On the basis of the known configuration of the β-asymmetric centers of the isomeric isoleucines, threonines, and phenylserines, a correlation between the configuration of this center and the extent of susceptibility of the α-asymmetric center to various L-and directed enzyme systems has been noted. (Winitz, Birnbaum and Greenstein). The findings with infra-red spectroscopy (Koegel, Greenstein, Winitz and Birnbaum) and rotatory dispersion (Otey, Greenstein, Birnbaum and Winitz) are described elsewhere in separate project reports.

Significance to cancer research:

Knowledge of substrate structure is of primary importance for an adequate understanding of the mode of enzymic action and function of normal and neoplastic tissues. Since all tissue proteins are composed of amino acids, knowledge of their subtle configurational differences as well as their gross structural differences thereby becomes essential. Use of physical, chemical, and biological means to ascertain such differences is the concern of this project.

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Continuation sheet

Proposed course of project:

Further studies on the effect of configuration of diassymmetric amino acids, in peptide linkage, on the action of various enzyme systems of normal and neoplastic tissue will consume a considerable proportion of the next calender year. The subject of the configurational relationship between the β-asymmetric center of natural isocitric acid and structurally related amino acids will also be pursued.

PROJECT REPORT FORM (Cont'd)

10. AI-307
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 27,455	6	0	6	3	0	3	
FY 1956	$ 18,550	5	0	5	2	0	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

15. ACI-307
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. J. P. Greenstein, N. Izumiya, M. Winitz and S. M. Birnbaum, J. Am. Chem. Soc., in press (Paper I).
2. M. Winitz, S. M. Birnbaum and J. P. Greenstein, J. Am. Chem. Soc., in press (Paper II).
3. M. Winitz, S. M. Birnbaum and J. P. Greenstein, J. Am. Chem. Soc., in press (Paper III).

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-308
SERIAL NO

ω-Acylases in normal and neoplastic tissues
PROJECT TITLE

7. Winitz, Birnbaum and Greenstein
PRINCIPAL INVESTIGATOR(S)

8. Bloch-Frankenthal
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives:

The objective of this project is to isolate, purify and study the specificity and adaptability of ω-acylases in normal and tumor bearing animals.

Methods employed:

Various tissues (kidney, liver, spleen, etc.) of a number of different organisms rat, mouse, pigeon, hog, guineau pig) are homogenized and the crude homogenate tested for the presence of an ϵ-acylase by its ability to hydrolyze ϵ-acetyl-L-lysine. Assay for free L-lysine in the enzymic digest is effected by subjecting such digest to the action of lysine decarboxylase and measuring the liberated carbon dioxide manometrically. Those crude homogenates which show activity are then subjected to ammonium sulfate or acetone fractionation procedures for the purpose of purification of the ω-acylases present therein.

Major findings:

The existence of one or more proteases capable of catalyzing the cleavage of peptide bonds involving the ϵ-amino group of L-lysine was suggested by observations that ϵ-acetyl-L-lysine is utilized in lieu of L-lysine as an essential amino acid in the diet of the rat. The occurrence of such enzyme (or enzymes?) in the tissues of several organisms (rat, hog, etc.) has recently been demonstrated in this laboratory. The enzyme system involved appears to have a hydrolytic pH optimum between 7 and 8 and is phosphate stabilized. Nutritional studies with laboratory animals have confirmed the previous finding that ϵ-acetyl-L-lysine may replace the underivatized amino acid in a lysine deficient diet.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-308

Continuation sheet

Significance to cancer research:

An adequate understanding of the differences in function that might exist between normal and neoplastic tissues requires, in part, a knowledge of the activity of the various enzyme systems that exist in these tissues. Knowledge of the action of such systems, as well as their requirements and specific inhibition, is prerequisite to an understanding of tissue synthesis and the general problem of growth.

Proposed course of project:

Since specificity studies of ω-acylases require the synthesis of a number of peptides involving both L- and D-amino acids in amide linkage with the ε-amino group of lysine and its analogs, considerable effort will be expended in this direction. Certain of these compounds will also be used in nutritional studies with laboratory animals to ascertain whether or not they are capable of fulfilling the lysine requirement in both normal and tumor bearing animals.

PROJECT REPORT FORM (Cont'd)

10. HL-308
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 13,[illegible]	4	0	4	1-1/2	0	1-1/2	
FY 1956	$ 9,275	3	0	3	1	0	1	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for 14, 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-309
SERIAL NO

6. Resolution of α,ε-diaminopimelic acid
PROJECT TITLE

7. Work (visiting scientist), Birnbaum, Winitz, Greenstein
PRINCIPAL INVESTIGATOR(S)

8. -----------
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
The preparation of the three stereoisomeric forms of α,ε-diaminopimelic acid in pure form in order to study their biological properties and their possible role in intermediary metabolism.

Methods Employed:
α,ε-Diaminopimelic acid was synthesized as a mixture of the D, L, and meso forms. Treatment of the amide derivatives of this mixture with an L-directed hog kidney amidase yielded a digest containing the L-amino acid, the D-diamide and meso half-amide. These forms were separated chromatographically.

Major Findings:
L-α,ε-Diaminopimelic acid with an optical rotation of +45.3° was prepared. The D-enantiomorph had an equal and opposite rotation while the meso form was optically inactive.

Significance to Cancer Research:
α,ε-Diaminopimelic acid has been found naturally occurring in various bacteria. It has been cited as a possible precursor of lysine in bacterial proteins (cf. Work). The fundamental study of protein metabolism is basic to the understanding of neoplastic growth.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

0. ACI-309
SERIAL NO.

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1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7325	3	0	3	1	0	1	0
FY 1956	0	0	0	0	0	0	0	0

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2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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3. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. 441-209
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

E. Work, S. M. Birnbaum, M. Winitz, and J. P. Greenstein, Separation of the Three Isomeric Components of Synthetic α,ε-Diaminopimelic Acid. J. Amer. Chem. Soc. In press.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-310
SERIAL NO

6. Chromatographic Techniques in the Study of the Homogeneity of Purified Proteins.
PROJECT TITLE

7. H. A. Sober and E. A. Peterson
PRINCIPAL INVESTIGATOR(S)

8. F. J. Gutter
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
To investigate the purity and homogenity of "pure" proteins.

Methods employed:
Chromatographic examination of "pure", crystalline proteins and examination of the resultant material by physical chemical criteria (i.e. electrophoresis, sedimentation, and solubility), by end group analyses, and by specific enzymatic and immunochemical activity.

Major Findings:
Proteins homogeneous by electrophoresis and sedimentation have been shown by chromatography to consist of several components. The relative distribution of these components is affected by storage and lyophilization. Preliminary examination by immunochemical techniques has indicated fractionation of immunochemical activities.

Significance to Cancer Research:
It is known that the "pure" proteins contain several detectable immunochemical, enzymatic or chemical species. Proteins isolated in specific pathological conditions, e.g. Bence-Jones protein from multiple myeloma urine, have been shown to be inhomogeneous by physical chemical criteria. For these pathologically elaborated proteins in particular, and for biologically active proteins in general, it is essential that methods and criteria be established to insure the unequivocal purity of the material in question when it is sought to relate the function of a given protein to its structure or composition.

Proposed Course of Project:
Additional crystalline proteins will be examined chromatographically and end-group

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-310

Continuation Sheet

and immunochemical analyses of the resultant fractions will be performed. Special emphasis will be accorded metallo-proteins and those with enzymatic properties.

PROJECT REPORT FORM (Cont'd)

10. M-310
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 11,580	3	2	5	1	1/3	1-1/3	
FY 1956	$ 11,048	3	2	5	1	1/3	1-1/3	

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12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

PROJECT REPORT FORM (Cont'd)

15. NCI-310
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Preparation and Properties of 2, 4 Dinitrophenyl-L - amino acids
by K. R. Rao and H. A. Sober
J. Am. Chem. Soc. 76,1328 (1954)

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Invited to present a Seminar before the Immunology-Communicable Disease Division Combined Seminar at the Army Medical Service Graduate School of Walter Reed Army Medical Center. October 7, 1954.
Title: Chromatography of Proteins on Cellulose Ion-Exchangers.
E. A. Peterson and H. A. Sober

Appointment of H. A. Sober as the N. I. H. representative on the Biophysics Study Section in the Division of Research Grants and on the Board of U. S. Civil Service Examiners for the National Bureau of Standards.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-311
SERIAL NO

6. Preparation and Evaluation of Various Cellulose Ion-Exchangers for Chromatographic Investigation of Proteins
PROJECT TITLE

7. E. A. Peterson and H. A. Sober
PRINCIPAL INVESTIGATOR(S)

8. - - - - - - - - - - -
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives

The objective of this project is to design and prepare adsorbents which permit the application of chromatographic principles to high molecular weight substances.

Methods Employed

Various acidic and basic groups are chemically attached to cellulose and the characteristics of these cellulose ion-exchangers with respect to adsorption and desorption of purified proteins is evaluated.

Major Findings

Ion-exchangers have been prepared from cellulose which have been shown to be effective adsorbents for the chromatography of typical proteins and deoxyribonucleic acids. The commercially available ion-exchange resins appear to be suitable only for relatively small molecules, including a few stable, atypical proteins of low molecular weight. A procedure has been developed which will permit systematic evaluation of adsorbents with regard to protein adsorption and will help in determining specific conditions for a given separation.

Significance to Cancer Research

Available methods for the examination of high molecular weight substances do not have sufficient resolving power to permit the isolation in purified form of the many different proteins which are known to exist from biological and immunological observations. Until suitable methods have been developed, the comparison of normal and abnormal enzymatic systems must necessarily only reflect gross rather than subtle changes in metabolic systems.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-311

Continuation Sheet

Proposed Course of Project.

The effect of the incorporation of different types and amounts of acid and basic groups and of the effect of the particle size of the absorbent will be investigated with reference to specific separation problems.

PROJECT REPORT FORM (Cont'd)

10. M-311
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 14,128	2	2	4	1-1/3	1/3	1-2/3	
FY 1956	$ 9,728	2	2	4	2/3	2/3	1-1/3	

2. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

3. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-311
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Chromatography of Proteins on Cellulose Ion-Exchangers, J. Am. Chem. Soc. 76 1711 (1954) by H. A. Sober and E. A. Peterson.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

(a) Invited participants at A Symposium on Recent Developments in Instrument Techniques and Applications, May 25, 1954, Bethesda, Md.
Title: Chromatography of Proteins with Cellulose Ion-Exchangers
by H. A. Sober, E. A. Peterson, and F. J. Gutter.

(b) The election of E. A. Peterson to the American Society of Biological Chemists, April, 1954.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-312
SERIAL NO.

6. Chromatographic Purification and Fractionation of Enzymes
PROJECT TITLE

7. E. A. Peterson and H. A. Sober
PRINCIPAL INVESTIGATOR(S)

8. F. J. Gutter and in collaboration with M. E. Maver and S. Birnbaum.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
To recognize, distinguish and isolate enzymes from various tissues with a view toward an understanding of the mechanism of action and of the specific structural relationships.

Methods Employed:
Chromatographic fractionation of crude or purified enzyme preparations by means of the new cellulose ion-exchangers and examination of the effluents by appropriate specific biochemical techniques.

Major Findings
Enzymes from spleen, heart, kidney, liver, and yeast have been purified and enzyme mixtures have been separated. Good recovery of enzyme activity has been obtained and in certain instances, resolution from the specific coenzyme. In addition, hitherto unrecognized enzyme specificites have been uncovered.

Significance to Cancer Research:
Proteins are key substances in the body and play a part in all activities of living matter. Among the proteins are the enzymes which selectively control and direct most of life's processes. An investigation of the enzymatic pattern of tissues in normal and abnormal situations requires techniques which permit the recognition and subsequent isolation of these components in pure form so that subtle differences can be detected and not overlooked due to dilution with or masking by contaminating systems.

Proposed Course of Project:
It is intended to continue the investigation of specific enzyme systems by purification and simultaneous substrate specificity studies in relation to

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-312

Continuation Sheet

coenzyme, metal and peptide components of the enzyme molecule.

PROJECT REPORT FORM (Cont'd)

10. 121-3/7
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 9,728	4	2	6	2/3	2/3	1-1/3	
FY 1956	$ 14,140	4	2	6	1-1/3	1/3	1-2/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

PROJECT REPORT FORM (Cont'd)

15. NCI-312
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

(a) Preparation of Crystalline Phosphorylated Derivatives of Vitamin B_6.
by E. A. Peterson and H. A. Sober
J. Am. Chem. Soc. 76 169 (1954)

(b) Studies on the Coenzyme Activation of Glutamic-Aspartic Apotransaminase
by A. Meister, H. A. Sober and E. A. Peterson
J. Biol. Chem. 206 89 (1954)

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

(a) Invited to Present a seminar at the Institute for Enzyme Research at Madison, Wisconsin, October 20, 1954.
Title: Chromatography of Proteins on Cellulose Ion-Exchangers
by E. A. Peterson and H. A. Sober.

(b) Invited to present a seminar at the Biochemistry Seminar of the University of Pittsburgh, November 4, 1954.
Title: Chromatography of Proteins by H. A. Sober and E. A. Peterson.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-313
SERIAL NO.

6. Chromatographic Analysis of Protein Components of Serum in Health and Disease
PROJECT TITLE

7. H. A. Sober and E. A. Peterson
PRINCIPAL INVESTIGATOR(S)

8. F. J. Gutter and J. H. Fahey
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
To develop and apply chromatographic procedures to the resolution and isolation of the many protein components in normal and pathological serum.

Methods Employed:
Serum and serum fractions are chromatographed on cellulose ion-exchangers and the effluent fractions are examined in terms of electrophoretic mobility, sedimentation, ultraviolet absorption, glucosamine and nitrogen content, and immunological activity.

Major Findings:
Whole blood serum and Red Cross serum fractions have been fractionated and there have been preliminary indications that immunological activity has been maintained as well as fractionated. Some 15-20 components have been recognized in serum by the application of the chromatographic method whereas only six components are detected by the usual electrophoretic techniques. Gamma globulins have been obtained free of the remaining serum proteins and have been further subdivided.
A pilot study of the chromatographic method in following the protein components in the serum of a single leukemic patient has been carried through from the first recognition of the disease to the terminal stages. Changes in individual components have been observed, but correlation with the course of the disease or with treatment has not yet been established.

Significance to Cancer Research:
A circulating fluid such as blood, which supplies nutrients and removes waste material, including proteins from necrotic tissue, from all parts of the body,

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-313

Continuation Sheet

must reflect in some manner alterations in tissue metabolism or composition which are the causes or consequences of disease. Hitherto examination of the protein composition of the blood has been restricted to either salting-out procedures or electrophoretic analysis. The latter technique separates serum into groups of proteins having different mobilities in the electric field. The chromatographic method, with the new cellulose ion-exchangers has already shown promise of being a more powerful tool, based on somewhat different principles, that will lend itself to the recognition and isolation of protein components of serum in diseased states.

Proposed Course of Project:
Two major lines of investigation will be pursued. 1. Emphasis will be placed on simpler elution schedules and improved fractionation in selected areas of the serum chromatograms, i.e. those which showed variation in the preliminary leukemic study. 2. Procedures will be sought for the large scale preparation of blood fractions which will permit retention and fractionation of immunochemical properties.

PROJECT REPORT FORM (Cont'd)

10. NCI -313
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$12,835	5	2	7	1	2/3	1-2/3	
FY 1956	$12,820	5	2	7	1	2/3	1-2/3	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

4

PROJECT REPORT FORM (Cont'd)

15. AC1-313
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Chromatography of Serum on Cellulose Ion-Exchangers
by E. A. Peterson and H. A. Sober. Fed. Proc. 13,273 (1954).

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

(a) Invited participants at the Gordon Research Conference for Ion Exchange, New Hampton, New Hampshire, July 21, 1954
Title: Chromatography of Proteins on Cellulose Ion-Exchangers, by E. A. Peterson and H. A. Sober.

(b) Invited Participants at the Seventh Annual Scientific Meeting of the Detroit Institute of Cancer Research, October 25, 1954, Detroit, Michigan.
Title: The Chromatography of Proteins by H. A. Sober and E. A. Peterson.

PROJECT REPORT FORM

National Cancer Institute
INSTITUTE

2. Biochemistry
LABORATORY OR BRANCH

Clinical Biochemical Research
SECTION OR SERVICE

4. Bldg. 10
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-314
SERIAL NO

Metabolism of Amino and Keto Acids; Studies on Amino Group Transfer
PROJECT TITLE

Meister
PRINCIPAL INVESTIGATOR(S)

Levintow, Otani, Fraser, Abendschein
OTHER INVESTIGATORS (Otani - Res. Fellow)

PROJECT DESCRIPTION

Objectives: To elucidate biochemical reactions and pathways of metabolism of amino acids in normal and tumor tissues, with emphasis on mechanisms of amino group transfer and keto acid metabolism, and if possible, to relate the results of *in vitro* studies to investigations on intact animals and man.

Methods: Tissues are fractionated by centrifugation, salt and ethanol precipitation, and adsorption and elution techniques to yield preparations which are active in catalyzing the reactions under study. Chemical, enzymatic, microbiological, and chromatographic procedures are employed in following these reactions. Substrates (metabolites or their analogues) such as amino or keto acids, peptides, etc., are prepared by synthetic organic procedures and by enzymatic methods. Isotopes such as N^{15}, C^{14}, and P^{32} are used in this work. Microbiological techniques, infrared and ultraviolet absorption studies, and polarimetry are also employed. Growth studies on rats using chemically defined diets have been carried out.

Major Findings: (Numbers in parentheses refer to references given below in #16)

A summary of our work on transamination and alpha-keto acids up to the first part of 1954 is given in reference (5). General reviews on transamination, and alpha-keto acid preparation have been given in references (11) and (9), respectively.

1. Although it has been known for some time that vitamin B_6 plays a role in amino group transfer, the mechanism of its action is not definitely known. Progress in this area has been reported this year (1): (a) For the first time it has been shown that pyridoxamine phosphate is a coenzyme of transaminase. Information concerning the binding of the coenzymes (pyridoxamine

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

Project Description (Cont.)

phosphate and pyridoxal phosphate) to the transaminase has been obtained by enzymatic studies and experiments with P^{32}-labelled coenzymes. The evidence supports a mechanism involving reversible Schiff base formation.

(b) The mechanism of inhibition of transamination by desoxypyridoxine has been studied. Desoxypyridoxine phosphate (prepared for the first time at N.C.I. by Peterson and Sober, J. Am. Chem. Soc., 76, 169 (1954)) inhibits transamination by competing with pyridoxal phosphate and pyridoxamine phosphate for the enzyme. The inhibitor is bound tightly by the protein, although less firmly than are the natural coenzymes. The significant point is this: Once the inhibitor is attached to the enzyme, the natural coenzymes cannot displace it--and--if a coenzyme is already attached to the enzyme, the inhibitor cannot displace it. The inhibitor would be expected to be more effective in a system with a high enzyme-coenzyme turnover than in one with a less rapid turnover.

2. Studies on the preparation and metabolism of alpha-keto acids have continued; with several interesting results (2,3,4):

(a) The alpha-keto analogue of cysteine, beta-mercaptopyruvic acid, is rapidly converted to sulfur (or, in the presence of certain reducing substances, e.g., glutathione, to hydrogen sulfide), and pyruvic acid. This is a new type of desulfuration reaction which may function in cysteine metabolism. The reaction takes place in a large number of tissues.

(b) The alpha-keto analogues of arginine, ornithine, and lysine were prepared for the first time. An enzymatic procedure employing L-amino acid oxidase of snake venom was used (3,8). Special blocking techniques were required for the preparation of alpha-keto analogues of lysine and ornithine in order to prevent cyclization. Certain biological and chemical properties of these compounds were studied. The alpha-keto analogue of arginine does not accelerate the growth of weanling rats given an arginine deficient diet, suggesting that the keto acid is not aminated at a rate compatible with optimal growth, or that the keto acid undergoes other reactions in vivo. In vitro studies indicate that arginine may be formed by transamination, and that ornithine transaminates with a number of alpha-keto acids to yield the corresponding amino acid and glutamic-gamma-semialdehyde. The reaction is unique in that the delta rather than the alpha amino group reacts. The reaction between ornithine and glyoxylate yielding glycine and glutamic-gamma-semialdehyde is also unique in that an aldehyde (rather than a keto acid) is both a reactant and product.

3. Investigations of asparagine and alpha-ketosuccinamate have been continued (7). The major finding has been that, under appropriate conditions, L-asparagine is synthesized in liver preparations by transamination of alpha-ketosuccinamate and a variety of L-amino acids. This is the first observation of asparagine synthesis on the enzymatic level. Further work is needed to establish whether this reaction is involved in the major biosynthetic pathway to asparagine.

4. A number of new substituted glutamines have been prepared including alpha-methylglutamine, beta-methylglutamine and, gamma-methylglutamine. In addition, the next higher homologue of glutamine, homoglutamine, and the next lower homologue of asparagine, alpha-aminomalonamic acid have been synthesized. A number of studies on these compounds are in progress.

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Project Description (Cont.)

Gamma-methylglutamine has been studied in the glutamine-alpha keto acid transamination system. Aothough gamma-methylglutamine transaminates readily with many alpha keto acids, there is no ammonia formed, and alpha-keto-gamma-methylglutaramic acid is a product. This finding gives considerable support to a 2 step mechanism for the glutamine-alpha-keto acid reaction, and to the concept that alpha-ketoglutaramic acid is an intermediate. It is of interest that substitution of glutamine with a gamma methyl group prevents deamidation, but has little effect on transamination.

Studies in progress include work on the structures of the 2 forms of alpha-ketoglutaramate and related compounds, experiments on related gamma glutamyl derivatives, and on the role of vitamin B_6 in the glutamine transaminase system.

Significance to Cancer Research: Tumors grow and accumulate amino acid nitrogen at the expense of normal tissues of the host. It is our feeling that an understanding of the amino acid metabolism of normal and tumor tissues will be of great importance in understanding the processes involved in tumor growth. The significant function of glutamate and glutamine in amino acid and protein metabolism justify intensive investigation of the biochemical properties of these and related compounds. A truly rational system of chemotherapy of cancer may develop when these fundamental processes are elucidated.

Proposed Course of Project: We plan to continue certain of the studies on transamination, to investigate the properties of the glutamine (and corresponding glutamic acid) analogues, and to extend this work to human tissues, if available. A number of exploratory studies in the clinical area are projected.

PROJECT REPORT FORM (Cont'd)

10. NCI-314
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$20,807	2	2	4	1 2/3	1	2 2/3	0
FY 1956	$20,776	2	2	4	1 2/3	1	2 2/3	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

PROJECT REPORT FORM (Cont'd)

15. NCI-314
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

(1) Meister, A., Sober, H. A., and Peterson, E. A.: Studies on the Coenzyme Activation of Glutamic-Aspartic Apotransaminase; Journal of Biological Chemistry, 206, 89, 1954.

(2) Meister, A., Fraser, P. E., and Tice, S. V.: Enzymatic Desulfuration of beta-Mercaptopyruvate to Pyruvate; Journal of Biological Chemistry, 206, 561, 1954.

(3) Meister, A.: The alpha-Keto Analogues of Arginine, Ornithine, and Lysine; Journal of Biological Chemistry, 206, 577, 1954.

(4) Meister, A.: Enzymatic Transamination Reactions Involving Arginine and Ornithine; Journal of Biological Chemistry, 206, 587, 1954.

(5) Meister, A.: The Enzymatic Transfer of alpha-Amino Groups; Science, 120, 43, 1954.

(6) Meister, A.: Studies on the Specificity and Mechanism of the Glutamine-alpha-Keto Acid Transamination-Deamidation Reaction; Journal of Biological Chemistry, 210, 17, 1954.

(7) Meister, A., and Fraser, P. E.: Enzymatic Formation of L-Asparagine by Transamination; Journal of Biological Chemistry, 210, 37, 1954.

(8) Meister, A.: The Use of Snake Venom L-Amino Acid Oxidase for the Preparation of alpha-Keto Acids - International Conference on Animal Venoms, AAAS (1954) In Press.

(9) Meister, A.: Preparation of alpha-keto Acids - Methods in Enzymology, Vol. II, Academic Press, New York, In Press.

(See continuation sheet)

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Paul-Lewis Award in Enzyme Chemistry of the American Chemical Society, April, 1954. (*cf* Reference (5)).

NCI-314

16. Publications (Cont.)

(10) Meister, A.: General Reactions of Amino Acids - in "Amino Acid Metabolism" - Pratt-McCallum Institute, Johns Hopkins University, Baltimore - In Press.

(11) Meister, A.: Transamination - Advances in Enzymology, Vol. XVI, Interscience, New York-London, In Press.

(12) Patent Still Pending: "Improvements in the Manufacture of alpha-Keto Acids."

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Clinical Biochemical Research
SECTION OR SERVICE

4. Bldg. 10
LOCATION (IF OTHER THAN BETHESDA)

5. ACI-315
SERIAL NO

6. Studies on Peptides in Normal and Cancerous Subjects
PROJECT TITLE

7. Baker and Levintow
PRINCIPAL INVESTIGATOR(S)

8. Moore and Itano (Moore - Res. Fellow)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The first objective is the development of methods which will allow identification and quantitation of peptides present in blood, urine and tissues. The second objective will be the collection of data on normal and cancerous subjects with a special emphasis on multiple myeloma. The ultimate objective is a better understanding of the role of peptides in protein synthesis, especially in terms of the synthesis of tumor proteins.

Methods Employed: Body fluids and tissue extracts are treated by different fractionation procedures to remove protein and other constituents, leaving the peptides in solution. These solutions are further fractionated by means of chromatographic procedures. By means of chromatography, end-group analyses and conventional methods of organic chemistry, including organic synthesis, identification and quantitation will then be attempted. Physico-chemical methods, including electrophoresis, will also be employed for studies in multiple myeloma.

Major Findings: In addition to the naturally-occuring amino acids, the behavior of 85 synthetic peptides in paper chromatography has been determined in 15 different solvent systems. On the basis of data obtained by these procedures, various conclusions regarding the relationship of chromatographic behavior and chemical structure have been made. Different methods of fractionating blood plasma have been employed, and preliminary chromatography studies have indicated that numerous peptides are present, though in small amounts.

Consideration of the kinetics of nitrogen metabolism has led to the development of differential equations related to a mathematical description for

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI- 315

9. Project Description (Cont.)

the cancer patient. Such equations were also developed independently by Dr. Donald Tschudy, and studies employing isotopically-labeled amino acids have been begun in conjunction with Drs. Tschudy, Watkin and Steinfeld on the kinetics of nitrogen metabolism in cancer patients.

Significance to Cancer Research: Since cancer tissue, as it grows, manufactures protein at an appreciable rate, and since it is primarily protein which gives uniqueness to a tissue, studies attempting to elucidate the process of protein formation, especially that in tumors, are of great importance. Peptides and amino acids, which are obtained from the partial breakdown of protein, appear to be involved in the formation of protein, and it has been reported that there is an increase in the peptides of the blood of cancer patients. More information on peptide and amino acid metabolism is therefore desirable. In the cancer bearing host, the cancer tissue utilizes nitrogen-containing compounds at the expense of other body tissues; these compounds must reach the tumor tissue by way of the blood stream. The peptides in the blood, therefore, need to be investigated as a possible source of tumor protein precursors. Multiple myeloma, which in many cases shows an abnormal protein in the blood and in the urine, provides an important means of studying protein metabolism in the tumor-bearing patient. The elucidation of the relationship of this protein to amino acid and peptide metabolism should provide important information about cancer protein metabolism.

Proposed Course of the Project: Considerable improvement in methods must be attained before data can be collected in comparisons between the normal and the cancer-bearing subject. The presence of large amounts of salts and the complex nature of many peptides make rapid progress difficult. By means of desalting devices and the use of various types of chromatographic resins it is expected that success will be achieved. The protein often found in urine of multiple myeloma patients contains an unusually high amount of serine and threonine and no methionine. Since it has been shown that homoserine is a common intermediate in the metabolic pathways for threonine and methionine, studies on this aspect of intermediary metabolism, with isotopic tracer techniques, along with the studies on amino acids and peptides are planned. It is also planned to investigate the role of peptides as protein precursors, and a comparison with other nitrogen-containing compounds will be made.

PROJECT REPORT FORM (Cont'd)

10. NCI-315
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$24,866	3	—	3	2 2/3	—	2 2/3	0
FY 1956	$24,733	3	—	3	2 2/3	—	2 2/3	0

12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

PROJECT REPORT FORM (Cont'd)

15. ACI-315
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

In Preparation.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Carl G. Baker was elected to the office of Secretary of the Division of Biological Chemistry of the American Chemical Society. He is also serving as an associate editor of the Journal of the National Cancer Institute.

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Clinical Biochemical Research
SECTION OR SERVICE

4. Bldg. 10
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-316
SERIAL NO

6. Studies of Mutant Forms of Hemoglobin
PROJECT TITLE

7. Harvey A. Itano
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To apply the methods of physical chemistry to the identification, fractionation, and characterization of abnormal human hemoglobins. To develop new methods to attain these ends.

Methods employed: Electrophoresis by the moving boundary and zone methods. Solubility determinations in concentrated salt solutions. Spectrophotometric determinations of rates and mechanisms of hemoglobin denaturation in alkali.

Major findings: Discovery of a fourth inherited abnormal human hemoglobin (E) and its characterization in terms of electrophoretic mobility, solubility, resistance to alkali denaturation, and ultraviolet spectrum. Two- or multi-step mechanism for alkali denaturation of human hemoglobin.

Significance to cancer research: One approach to the cancer problem is the study of mutations. The abnormal hemoglobins result from mutant genes in humans, and the elucidation of the properties and structures of these hemoglobins may shed some light on the underlying basis of mutations.

Proposed course of project: Continuation of basic research along the lines outlined above. Continued collaboration in clinical research with internists, pediatricians, and hematologists interested in the abnormal hemoglobin problem.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. AC1-316
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$6,216	1	—	1	2/3	—	2/3	0
FY 1956	$6,183	1	—	1	2/3	—	2/3	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

15. 161-316
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. Itano, H. A., Bergren, W. R., and Sturgeon, P., Identification of a Fourth Abnormal Human Hemoglobin, J. Am. Chem. Soc. 76, 2278 (1954)

2. Bergren, W. R., Sturgeon, P., and Itano, H. A., Zone electrophoresis of abnormal hemoglobins. Separation on paper of hemoglobins associated with sickle cell disease. Acta Haematologica, 12, 160-168 (1954)

3. Sturgeon, P., Itano, H. A., and Bergren, W. R., Clinical Manifestations of inherited abnormal hemoglobins: I. The interaction of hemoglobin-S with hemoglobin-D. II. Interaction of hemoglobin-E with thalassemia trait.

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

1. H. A. Itano. Eli Lilly and Company Award in Biological Chemistry for 1954.

2. H. A. Itano. Accepted invitation to deliver the George Minot Lecture for the Section on Experimental Medicine and Therapeutics of the American Medical Association on June 18, 1955.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Clinical Biochemical Research
SECTION OR SERVICE

4. Bldg. 10
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-317
SERIAL NO

6. Glutamine Metabolism
PROJECT TITLE

7. L. Levintow, A. Meister, ~~P. Fraser, P. Abendschein~~
PRINCIPAL INVESTIGATOR(S)

8. P. Fraser, P. Abendschein
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This project is concerned with investigation of the biosynthesis and metabolic role of glutamine and related compounds, and observation of the effect of the neoplastic transformation upon these metabolic pathways.

Methods Employed: Soluble enzymes are extracted and purified from normal and neoplastic tissues, and the reactions catalyzed by these enzymes are studied *in vitro*, employing chemically characterized substrates. In addition, metabolic routes in the intact organism are studied by the administration of metabolic intermediates, isotopically labelled in some instances.

Major Findings: (Reference numbers are given in parentheses, see point 16)

1. A significant finding was that the enzymatic synthesis of glutamine from glutamic acid, ammonia, and adenosine triphosphate is a freely reversible reaction (1) Thus, the amide bond of glutamine may be a source of energy for adenosine triphosphate synthesis. Furthermore, detailed study of this equilibrium has led to a determination of the standard free energy change in the reaction, and to a revised value of the free energy of hydrolysis of adenosine triphosphate. Our studies suggest that a value of -8000 calories is closer to the true value, than the currently accepted figure of about -10,500 calories.

2. The conversion of glutamine to gamma-glutamylhydroxamate was studied in 14 normal and 23 neoplastic tissues of the rat and mouse (2). Many of the tumors exhibited low activity; however, activity levels for higher than liver or brain (or any other normal tissue studied) were found with several mouse hepatomas.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-317

Project Description (Cont.)

3. A glutamine-requiring mutant of Aerobacter aerogenes is currently being investigated. It is interesting that this organism catalyzes gamma-glutamylhydroxamic acid formation from glutamine at a much faster rate than does the wild type of origin. The significance of this finding, and other aspects of this problem, are being studied.

4. Procedures for the preparation of purified glutaminase, asparaginase, and a new liver omega-amidase have been developed. The latter system is unique in that it catalyzes hydrolysis of alpha-ketoglutaramic acid and several related compounds, but does not act on glutamine. Furthermore, the new amidase catalyzes transfer reactions at a much more rapid rate than the rates of hydrolysis. The significance of these findings in relation to the mechanism of enzyme action, and to the mode of amide bond synthesis (e.g. asparagine) may be considerable, and the subject is being pursued.

5. Studies on a variety of glutamine analogues are in progress. These include methyl and hydroxyl substituted derivatives of glutamine. The effects of these derivatives at the enzymatic level and on the intact organism are being determined.

Significance to Cancer Research: We interpret recent findings as strong evidence that glutamine is an important intermediate not only in amino acid and peptide metabolism, but in purine synthesis as well. Study of a compound which may stand at the crossroads leading to proteins on the one hand and to nucleic acids on the other would appear to offer unique opportunities for the elucidation of possible interrelationships of these two classes of compounds, each of which plays a basic role in growth processes. It is of importance that folic acid or a related compound is required for purine synthesis. This aspect of the problem and the effects of antifolic acid derivatives are of great interest in this work, and may lead to important relationships significant to the conduct of clinical chemotherapeutic experiments.

Proposed Course of the Project: It is proposed to continue investigation of the mechanism by which the dephosphorylation of ATP leads to the formation of the amide bond of glutamine. Also to be continued are studies of a variety of enzymatic reactions of glutamine and related compounds, on both the synthetic and degradative pathways, in normal and neoplastic tissues. Glutamine is the largest amino acid constituent of human blood, a finding consistent with a significant role in human metabolism; investigations on the clinical level are anticipated.

PROJECT REPORT FORM (Cont'd)

10. LCI-317
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 11,482	2	2	4	2/3	1	1 2/3	—
FY 1956	$ 11,501	2	2	4	2/3	1	1 2/3	—

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

PROJECT REPORT FORM (Cont'd)

15. ACI-317
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

(1) Levintow, L., and Meister, A.: Reversibility of the Enzymatic Synthesis of Glutamine, J. Biol. Chem. 209, 265, 1954.

(2) Levintow, L.: The Glutamyltransferase Activity of Normal and Neoplastic Tissues, J. Natl. Cancer Inst. 15, 347 (1954)

(3) Meister, A.: Glutaminase, Asparaginase, and alpha-keto acid omega-amidase, Methods in Enzymology, Vol. I, Academic Press, New York - In Press.

(4) Meister, A., Levintow, L., Greenfield, R. E., and Abendschein, P. A., Hydrolysis and Transfer Reactions Catalyzed by omega-Amidase Preparations, J. Biol. Chem., In Press.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

L. Levintow was elected to membership in the American Chemical Society and the American Society of Biological Chemists.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Enzyme and Metabolism Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-318
SERIAL NO

6. Comparative studies on the metabolism of catalase and other heme proteins in normal and tumor-bearing animals.
PROJECT TITLE

7. Drs. Vincent E. Price and Robert E. Greenfield
PRINCIPAL INVESTIGATOR(S)

8. none
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study and compare the relative rates of incorporation of radioactive iron into the ferritin, catalase, and hemoglobin of normal and tumor-bearing animals.

Methods Employed: Comparative time studies will be made in order to follow the rate of incorporation of Fe^{59} into the ferritin, catalase, and hemoglobin of normal and tumor-bearing animals. Ferritin, catalase, and hemoglobin will be isolated in pure form and their specific radioactivities determined. Measurements of blood volume, alkaline hematin, hematocrit, catalase activity, storage iron, and total iron will be carried out to assist in the evaluation of the radioactive tracer data. If possible a tumor growing in a highly inbred strain of rats will be used so as to reduce the random variation and make any differences between normal and tumor-bearing rats more definitely significant. The use of an ascites tumor is also being considered so that a uniform tumor-cell inoculum can be implanted in the rats to be studied so that a more uniform tumor growth can be obtained.

Major Findings: This project is just being initiated. Initial studies show that a marked anemia frequently accompanies the lowered liver catalase. However, in rats with rapidly growing intraperitoneal tumors a markedly lowered catalase without anemia may be observed. It seems that both the anemia and the reduced liver catalase may be manifestations of a similar defect in porphyrin metabolism and that the degree of the anemia and catalase reduction may depend on the site of the tumor in the host.

Significance to Cancer Research: The anemia and cachexia of cancer patients

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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is well known and illustrates, to an extreme, that the body of the host with its delicately balanced biochemical mechanisms may provide a sensitive tool by which to discover, measure, and identify abnormal products from the tumor which in amount or type represent its unusual metabolism. An understanding of these altered mechanisms will be of value in developing diagnostic procedures and specific approaches to chemotherapy.

Proposed Course of Project: Time studies will be made comparing the rates of incorporation of iron into ferritin, catalase, and hemoglobin at various intervals after the injection of Fe^{59} in normal and tumor-bearing animals. Further studies will be carried out at various stages of tumor development to follow the kinetics of the various changes.

PROJECT REPORT FORM (Cont'd)

10. 61-318
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$17,224	2	3	5	1	1-1/2	2-1/2	
FY 1956	$16,956	2	4	6	1	1-2/3	2-2/3	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Enzymes and Metabolism Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-319
SERIAL NO

6. Studies on the Catalase-reducing Factor in Tumors.
PROJECT TITLE

7. Drs. Robert E. Greenfield and Vincent E. Price
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
To understand the mechanism by which tumors interfere with catalase metabolism.

Methods Employed:
Isolation and characterization of the tumor factor by chemical and chromatographic separation. These biologically active fractions will be isolated and studied from various sources such as malignant tissues, ascites tumor fluid, plasma, and urine of tumor-bearing animals and patients.

Major Findings:

Dr. Greenstein's original studies on the reduction of liver catalase by tumors have been extended by ethanol fractionation of tumor homogenates to obtain a fraction which will rapidly reduce the liver catalase activity of mice on intraperitoneal injection.
Preliminary studies have shown that the feeding of tumor for 72 hours will lower liver catalase to a considerably greater extent than the feeding of normal tissues. This suggests that the tumor factor is not destroyed by the intestinal enzymes and can readily be absorbed through the intestinal wall.
Further studies have indicated that the cell-free fluid from ascites tumors may contain factors which will reduce liver catalase activity on injection intraperitoneally into normal animals.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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Significance to Cancer Research:

Isolation of this factor will permit a better understanding of the mechanism by which tumors alter the metabolism of the host. It may also provide a clue to an abnormal pathway of metabolism in cancer cells. Finally, it may lead to a sensitive diagnostic procedure for cancer.

Proposed Course of the Project:

An attempt will be made to isolate the tumor factor from cell-free ascites fluid, plasma, or urine in the hope that the tumor factor may be in a free state and more readily separated from the simpler components of these fluids than from the complex components of malignant tissue. Isolation from these sources should also decrease the possibility of artifacts as the drastic hydrolyses used in releasing the factor from tumor tissue will probably not be necessary. Such hydrolyses might produce active fractions which would not be released into the blood stream by the tumor.

PROJECT REPORT FORM (Cont'd)

10. NC1-319
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7295	2	3	5	1/2	1/2	1	
FY 1956	$11,501	2	3	5	2/3	1	1-2/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Enzymes and Metabolism Sect.
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. [illegible]-320
SERIAL NO

6. Isolation and Characterization of Liver Catalase of Normal and Tumor-bearing Animals.
PROJECT TITLE

7. Drs. Robert E. Greenfield and Vincent E. Price
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:

1. Localization of catalase in the particulate fractions of rat liver (completed)
2. Electrophoretic studies on catalase from normal and tumor-bearing animals (with Dr. H. Itano).

Methods Employed:

1. Isolation of catalase from particulate fractions using sucrose and the high polymer, polyvinylpyrrolidone, to protect the integrity of the mitochondria.
2. Electrophoretic studies on very pure fractions of catalase from normal
a and tumor-bearing animals to see if any difference in electrophoretic mobility can be observed.

Major Findings:

1. Catalase isolated in sucrose solutions is progressively eluted from the mitochondria into the supernatant where it rapidly declines in activity.
2. If the particulate fractionation is carried out in polyvinylpyrrolidone-sucrose solutions nearly all of the catalase remains in the mitochondrial fraction.
3. If catalase is first eluted from the mitochondria with sucrose addition of polyvinylpyrrolidone will not cause coprecipitation of the catalase with the mitochondrial fraction.
4. Intact particulates exhibit little catalase activity. The maximum activity can be measured only after disruption of the mitochondria with ammonium sulfate.
5. Although the total catalase activity in the liver of tumor-bearing animals is markedly reduced, the specific activity of catalase isolated directly

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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Continuation Sheet

from the mitochondria is very high and nearly the same as that isolated from normal liver mitochondria.

6. When newly-formed catalase is isolated from regenerating liver, it is not significantly higher in activity than that obtained from liver of normal and tumor-bearing animals. This suggests that in the mitochondrial catalase is uniformly of a very highly active form and does not degenerate to a less active state during its life span in either the normal or tumor-bearing animals.

Significance to Cancer Research:

In view of the marked reduction of liver catalase in tumor-bearing animals described by Dr. J. P. Greenstein and coworkers, it seemed important to learn whether the liver catalase of tumor-bearing animals was simply reduced in amount or whether an altered catalase characteristic of tumor-bearing animals might be present.

Our earlier studies showed that the amount of catalase present in the liver of tumor-bearing animals was markedly reduced.

Although the sedimentation and spectral characteristics of the remaining catalase was the same as that of normal liver, the specific activity of the catalase from tumor-bearing animals was markedly reduced and it seemed possible that the ability of tumor-bearing animals to form the highly active catalase found in normal animals was reduced or absent. In view of the findings described above, it now appears that the liver catalase of both normal and tumor-bearing animals is of uniformly high specific activity if isolated directly from the mitochondria. If catalase is first eluted into the supernatant, it rapidly loses activity.

The localization of catalase in the mitochondria is not only of general interest in field of cellular chemistry but also will be of considerable value in our future studies on the mechanism by which tumors lower liver catalase. It is quite possible that if a block in the pathway of catalase synthesis occurs in tumor-bearing animals then precursors of catalase might be found to accumulate in the mitochondria.

Proposed Course of Project:

Electrophoretic studies on hemoglobin have demonstrated the value of this tool in the separation and characterization of this heme protein. In view of the excellent isolation procedures now available to us it will be valuable to carry out electrophoretic studies on catalase isolated from livers of normal and tumor-bearing animals. These studies are being planned with Dr. Harvey Itano.

PROJECT REPORT FORM (Cont'd)

10. 151-326
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	[illegible]	2	3	5	1/2	1	1-1/2	
FY 1956	$4,865	3	2	5	1/3	1/3	2/3	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

15. M1-820
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Liver Catalase I. A Manometric Determination of Catalase Activity. Robert E. Greenfield and Vincent E. Price, Jour. Biol. Chem. 209, 355, 1954.

Liver Catalase II. Catalase Fractions from Normal and Tumor-bearing Animals. Vincent E. Price and Robert E. Greenfield, Jour. Biol. Chem. 209, 363, 1954.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

none

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Enzymes and Metabolism
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-321
SERIAL NO

6. Metabolic Studies on the β-Hydroxy-α-amino Acids in Normal and Tumor Tissues
PROJECT TITLE

7. J. B. Gilbert
PRINCIPAL INVESTIGATOR(S)

8. ---------
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
The object of this project is to delineate more clearly; the synthesis and breakdown of the β-hydroxy-α-amino acids, with particular reference to the essential amino acid, threonine, in normal and tumor tissue.

Methods Employed:
For the assay of the end products of the enzymatic reactions, numerous techniques are employed. These include chromatography and colorimetric and spectrophotometric methods. Radioactive compounds are also used as an aid in mapping the metabolic pathways. For enzyme preparation, centrifugation, precipitation by salts and differential elution of tissue extracts have been used.

Major Findings:
The major finding of this project during the past year has been the in vitro synthesis of the "essential" amino acid threonine from glycine and acetaldehyde in the presence of a rat liver enzyme.

Significance to Cancer Research:
The finding described above is of considerable significance to cancer research. Since threonine is described as an "essential" amino acid, and as we now have evidence of in vitro formation of threonine by mammalian tissue from normal metabolic precursors,

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CONTINUATION SHEET

the nutritional status of the amino acid needs further examination. The nutritional problems in the patient with cancer are indeed critical. A determination of just how "essential" threonine is would contribute to this important alimentary and metabolic problem.

Proposed Course of Project:

The initial portion of this coming year will be devoted to a definitive characterization of the enzymatic reaction forming threonine. Beyond that a test of enzymatic synthesis of serine, phenylserine and β-hydroxynorvaline from glycine and suitable aldehyde is desirable in order to examine the generality of the reaction.

In addition, trial of *in vivo* synthesis of threonine from acetaldehyde and glycine is contemplated, which may well prove significant in the nutritional problems of cancer patients.

PROJECT REPORT FORM (Cont'd)

10. Mcl-321
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$11,080	1	1	2	1	1/3	1-1/3	
FY 1956	$11,048	1	1	2	1	1/3	1-1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

15. [illegible]1-321
SERIAL NO.

---

6. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

James B. Gilbert. Stereochemical Specificity of Enzymatic Cleavage of β-Phenylserine. J. Am. Chem. Soc., 76, 4183 (1954).

John Z. Hearon and James B. Gilbert. New Methods for the Calculation of Association Constants of Complex Ion Systems. J. Am. Chem. Soc. In press.

James B. Gilbert, M. Clyde Otey and John Z. Hearon. Association Constants of Cobalt-glycine and Cobalt-glycylglycine Complexes in Aqueous Solution. J. Am. Chem. Soc. In press.

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7. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Enzymes and Metabolism
SECTION OR SERVICE

4. LOCATION (IF OTHER THAN BETHESDA)

5. NCI-322
SERIAL NO

6. Studies on the Purification and Characterization of Nucleases and Cathepsins of Normal and Neoplastic Tissues
PROJECT TITLE

7. Mary E. Maver
PRINCIPAL INVESTIGATOR(S)

8. E. A. Peterson, H. A. Sober, and A. Greco
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
The objective of this project is to obtain active preparations of the various cathepsins, desoxyribonucleases and ribonucleases from normal and neoplastic tissues in order to compare (1) the rates of hydrolysis on their respective substrates and (2) the types of hydrolytic products formed.

Methods:
The cathepsin and nuclease preparations are separated from tissue homogenates by fractional centrifugation, dialysis, ammonium sulfate and cold alcoholic precipitations at the optimal pH. At an early stage in this procedure practically all of the catheptic activity is separated from the desoxyribonuclease and ribonuclease. Further purification of the fractions is obtained by chromatography. The enzymes are characterized by the rates at which they hydrolyze appropriate substrates.

Major Findings:
The cathepsins as prepared from spleen, normal liver and hepatoma have been characterized as the C type with marked transpeptidase activity. The spleen desoxyribonuclease digested DNA to give products with increased absorption at 260° over the undigested DNA. The spleen ribonuclease preparation hydrolyzed the cyclic $C_2'-C_3'$ phosphate esters of cytosine and adenosine to give the C_2' phosphate esters while the pancreatic ribonuclease reacts very slowly and yields the C_3 phosphate esters.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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CONTINUATION SHEET

Significance to Cancer Research:
The enzyme systems studied in this project are related to the rapid protein synthesis and cell division which are generally characteristic of tumor growth. The cathepsins are proteolytic enzymes which function in the metabolism of proteins whose rapid synthesis is reflected in tumor growth. The nucleases are also related to cellular metabolism since it has been reported that the turnover of desoxyribosenucleic acid is 10 times more rapid in tumors, while the turnover of ribosenucleic acid is twice as rapid as in normal tissues.

Proposed Course of Project:
It is planned to continue studies on the characterization of the cathepsin preparations from different tissues. Further studies will be made to perfect a technique for determination of nuclease activities of fractions from the chromatographic column. It is also planned to characterize the nucleases of different tissues by studying the products of their digestion of nucleic acids qualitatively by paper chromatography.

PROJECT REPORT FORM (Cont'd)

10. NCI-322
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 19,857	3	3	6	1	2	3	
FY 1956	$ 11,501	1	2	3	2/3	1	1-2/3	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Enzymes and Metabolism
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-323
SERIAL NO

6. Chemical Composition of C3H Hepatomas as Related to Growth and Transplantability
PROJECT TITLE

7. Mary E. Maver
PRINCIPAL INVESTIGATOR(S)

8. H. Andervont, R. J. Koegel and A. E. Greco
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
To determine whether differences in chemical composition, as determined by their content of water, total lipid, nitrogen, phosphorus, potassium and sodium, can be correlated with differences in the growth rates of the tumors, or with their ability to grow when transplanted.

Methods:
Spontaneous hepatomas in C3H mice are analyzed chemically, verified histologically as hepatomas, and each tumor transplanted into 4 to 6 mice. When transplants have grown they in turn are analyzed chemically and one tumor is transplanted into 4 to 6 mice.

Major Findings:
Of 6 original spontaneous hepatomas transplanted 18 months ago, the transplants of 3 have grown and have been transplanted twice. (One of these has changed to a sarcoma.) The transplants from 2 of the original tumors have grown more slowly and have been transplanted once, and one transplant has not grown at all in 5 mice. There was some indication that tumors with relatively higher lipid content did not grow on transplantation.

Significance to Cancer Research:
This study is of significance to cancer research because it will add to our basic knowledge concerning the chemical properties of tumors in inbred mice, whether or not we find a definite correlation between the chemical analyses and the rates of growth

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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and transplantability. Very few, if any, studies of this type using inbred strains of mice and the latest techniques (flame photometry) for sodium and potassium analysis have been reported.

It has been suggested that similar chemical analysis of human tumors after surgery might furnish a prognosis as to the rate of growth and malignancy of subsequent metastases.

Proposed Course of Project:

The transplantation of the tumors will be continued until their rates of growth have become stabilized. When the chemical analysis of the tumors has been completed an attempt will be made to correlate the chemical data with growth rates and transplantability.

10. Ad-323
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$9,928	3	2	5	1/2	1	1-1/2	
FY 1956	$9,956	3	2	5	1/2	1	1-1/2	

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-324
SERIAL NO

6. Biological Studies of the Carcinogenic Action of 2-Acetylaminofluoren (2-AAF) and Related Compounds
PROJECT TITLE

7. H. P. Morris
PRINCIPAL INVESTIGATOR(S)

8. Billie P. Wagner
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective:
A study of the influence of chemical structure upon induction of cancer including the carcinogenic activity of metabolites of known chemical carcinogens.

Methods Employed:
Known chemical compounds are incorporated into the diet at equimolar concentration and fed to rats of both sexes and of different strains. The animals are carefully necropsied, the tissues fixed, sectioned, stained and eventually examined microscopically for evaluation of microscopic tissue changes. Experiments were started within the year to test the following compounds:

3,4-Xylidine - a dimethylaromatic amine
3,3'-Diacetyldiaminobiphenyl
4,4-4',4'-Tetramethyldiaminobiphenyl
2,2'-Diacetylaminobiphenyl
2-Benzoylaminofluorene-2'-carboxylate
2-(4'-Methyl)-benzoylaminofluorene
2-(3'-Methyl)-benzoylaminofluorene
2-(2'-Methyl)-benzoylaminofluorene

The biological results of these tests will not be available for approximately another year.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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CONTINUATION SHEET

Compounds started on test in late 1952 have been completed and a preliminary or partial preliminary microscopic pathologic examination was completed during the year. The following 11 compounds were tested:

1-Acetylaminofluorene - slightly carcinogenic
1-Diacetylaminofluorene - slightly carcinogenic
2-Acetylaminofluorenone - very carcinogenic to breast and to several other sites
4,4'-Diacetylaminobiphenylsulfone - slightly carcinogenic
4'-Fluoro-4-acetylaminobiphenyl - highly carcinogenic liver, breast, and kidney
3'-Methyl-4-acetylaminoazobenzene - slightly carcinogenic
4-Acetylaminoazobenzene - slightly carcinogenic
2,7-Dibenzoyldiaminofluorene - slightly carcinogenic
3-Acetylaminofluorene - incomplete, but is carcinogenic
7-Methoxy-2-acetylaminofluorene - carcinogenic
2-Trifluoracetylaminofluorene - very carcinogenic at several sites

Distant tumors were produced by all the compounds tested but only two were highly carcinogenic, i.e. equal to or more carcinogenic than 2-acetylaminofluorene, the reference carcinogen.

Significance to Cancer Research:
The biological testing program provides an essential index of carcinogenic potency of chemical compounds which may be produced *in vivo* during metabolism of chemical carcinogens or related to structural changes which the compounds may undergo during their degregation by the animal. The discovery of new carcinogens provides new pathways for studying metabolism of chemical carcinogens by the isotopic tracer and other techniques developed for that purpose in this section and will aid in a more complete understanding of the mechanisms by which cancer can be induced by known chemical compounds. It is believed these investigations will help explain the origin of cancer especially the changes which take place prior to the detection of a definitive tumor.

Proposed Course of Project:
As indicated above a large number of potential metabolites are currently under test in continuation of objectives of the project. Additional compounds will be tested as they are made available, and as the work load will permit. A synthetic organic chemist would push the program forward more rapidly. The immediate goal is to prepare for publication the material now nearing completion.

PROJECT REPORT FORM (Cont'd)

10. M1-324
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$20,460	1	4	5	1/2	3	3-1/2	
FY 1956	$24,592	1	4	5	1/2	3	3-1/2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. NCI-324
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

J. H. Weisburger, E. K. Weisburger, and H. P. Morris. The Effect of Riboflavine on the Metabolism of 2-Acetylaminofluorene-9-C^{14} in Rats. J. Nat. Cancer Inst., 15, 37 (1954).

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

Nutrition and Carcinogenesis
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-325
SERIAL NO

Mechanism of Carcinogenesis: Metabolism of Acetylaminofluorene and Related Compounds.
PROJECT TITLE

Helen M. Dyer
PRINCIPAL INVESTIGATOR(S)

Collaboration with Harold P. Morris and Mary E. Maver is planned.
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objective: To further relate the chemical structure and the metabolic behavior of 2-acetylaminofluorene (2-AAF) to its carcinogenic activity with the hope of explaining why 2-AAF is a potent cancerogenic agent while some structurally related compounds are not.

Methods employed: *In vivo* experiments have been and are being carried on, in which 2-AAF and related nitrogen-containing carcinogenic and noncarcinogenic compounds are administered to rats and their metabolic behavior is studied by analysis of the tissues and the excreta. Special methods (with N-15 enriched compounds) have been used for identification and quantitative determination of metabolites.
Guinea pigs have been used in parallel experiments to compare the metabolism of 2-AAF in a relatively cancer-resistant species to that in the susceptible rat.
In vitro studies have been made to investigate further the metabolic behavior of these compounds.

Major Findings: Excretory products from 2-AF and related compounds: Some correlation was found between the degree of carcinogenicity (especially for the liver) to rats of various substituted derivatives of 2-AAF when the substituent groups were in the amino portion of 2-amino compounds and (1): the amount of diazotizable R-salt-coupling material excreted in the urine and (2) the oxidation of the compounds to 7-OH-2-AAF.
No correlation was found between carcinogenic potency and the amounts of urinary diazotizable material and the oxidation to phenolic derivatives of amino fluorene compounds other than those in the 2-position.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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Continuation Sheet

Two derivatives of 2-AF that have been found by Morris to be little, if any carcinogenic, were found to be excreted in the feces unmetabolized after oral administration, and in the peritoneal cavity unabsorbed after intraperitoneal administration.
Two iodo derivatives of 2-AF, that have been found to differ strikingly in degree of carcinogenicity, were found to be different in the excretion of conjugated and free amines.
The metabolic behavior of 2-AAF and 3-AAF in the rat with respect to the amounts of ortho-hydroxy metabolites formed does not support Clayson's working hypothesis that aromatic amines, in general, like B-naphthylamine, are carcinogenic to those species in which the major metabolites, quantitatively, are the ortho-hydroxy derivatives.
The urinary excretion of diazotizable and phenolic material following administration of 2-AAF to the guinea pig is similar to that of the rat.
In carrier experiments with 2-AAF-N^{15} , 10-15 percent of administered AAF could be accounted for in the ether extract of the urine as AF, AAF and 7-OH-2-AAF. After treatment with B-glycuronidase and takadiastase 84 percent of the preferentially water-soluble isotopic nitrogen of the urine became ether soluble indicating that it had been present as conjugates of phenolic derivatives of AAF.

Protein binding studies: In protein binding studies, using 2-AAF enriched with isotopic nitrogen there was found in two crude protein fractions isolated from the livers of rats a small but consistent excess in concentration of isotopic nitrogen compared with corresponding fractions from untreated rats. With dosages that cannot be exceeded without acute toxicity it seems to be impossible to indrease the concentration of isotopic nitrogen in the "proteins". The disappearance of "bound" nitrogen parallels the rate of turn over of liver proteins.
No N^{15} binding could be detected in the proteins from the liver of guinea pigs following administration of 2-AAF-N-15.
N^{15} binding was not detectable in corresponding protein fractions from lungs, spleen, brain, heart, abdominal skin and abdominal muscle from rats whose liver proteins showed enrichment. Protein fractions from kidneys and small intestines sometimes showed enrichment, and some excess isotopic nitrogen was found in the proteins of spontaneous mammary tumors and of a spontaneous hepatoma, but little, if any was detectable in the protein material from subcutaneous and intramuscular transplants of hepatomas and cholangiomas after feeding the material to the hosts.
In vitro studies, in which liver homogenates and slices were incubated with N-15 enriched carcinogen, demonstrated that the protein binding of the nitrogen was quantitatively the same in vitro as in vivo when super saturated substrates were used. 2-AF gave higher ratios of isotopic nitrogen than 2-AAF and the protein fractions isolated from homogenates higher than those from slices. The proteins from homogenates and slices of guinea pig livers did not show bound isotopic nitrogen and those from similar preparations of transplanted liver tumors did not bind as much as the proteins of the livers of the hosts. Coagulated albumin following the incubation of 2-AF-N-15 or 2-AAF-N-15 with solutions of crystalline bovine plasma albumin did not show any binding of isotppic nitrogen.

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Continuation Sheet

Attempts to remove the isotopic nitrogen from the proteins by various organic and inorganic solvents have failed.
In vivo and *in vitro* studies have demonstrated that 2-AAF is not deacetylated by the gastric juice of rats.
It has been found that a trace of isotopic nitrogen is present in the urine of the rat as ammonia during the first 48 hours following administration of 2-AAF-N-15 and of 2-diacetyl-AF-N-15 but not after a milliquivalent dose of 2-nitrofluorene-N-15.

Significance to Cancer Research: If the fundamental change in normal cells which creates neoplastic ones is the same for all kinds of neoplasms (arising from different known or unknown stimuli) then the studies undertaken in this project may ultimately help to throw some light on the mechanism of carcinogenesis. If the mechanisms are different for different agents then any significant findings that may result from these investigations will be limited to the mechanism of the chemical under study.

Proposed course of project: When compounds related to aminofluorene have been studied by Dr. Morris for their carcinogenic potency their fate in the animal body will be followed with methods and necessary modifications of the methods used above.
When N^{15} enriched materials are available, particularly of 3-AAF and 4-AAF which have little ability to induce tumors, their fate in the body with regard to excretion and protein binding will be compared with that of 2-AAF. It is hoped that we shall be able to synthesize some of the desired N-15 enriched compounds and some long-wanted metabolite suspects here.
I have proposed to compare the binding of isotopic nitrogen by cathepsins and nucleases with the effect to 2-AAF on the enzyme activities. This will be undertaken in collaboration with Dr. Mary Maver of the Enzyme Section of the Laboratory of Biochemistry.
Further work is planned on studies that have been started, designed to provide optimum conditions for the *in vitro* metabolism of 2-AF and/or 2-AF. Thus far, changing of buffers and addition of supplements have done little to increase the small amount of demonstrable acetylation and deacetylation. Oxidation has not been demonstrated *in vitro*, and that too is an objective. Future investigation is to be directed to studying the effects of the carcinogen upon the normal activities of the tissues rather than to the effect of the tissues upon the carcinogen.

PROJECT REPORT FORM (Cont'd)

10. M1-325
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$14,591	1	1	2	1	1	2	
FY 1956	$ 14,593	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

15. NC1-325
SERIAL NO.

None since October 1953.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

7. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Relating to this research only in part: Alumni Award Goucher College, April, 1954 at dedication of new Science Building.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis
SECTION OR SERVICE
Enzymes and Metabolism

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-324
SERIAL NO

6. In Vitro and In Vivo study of the Effect of Carcinogens on the Activities of Cathepsin and Nucleases of Tissues.
PROJECT TITLE

7. H. M. Dyer and M. E. Maver
PRINCIPAL INVESTIGATOR(S)

8. A. E. Greco
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective:
To determine whether carcinogens function by combining with the protein of enzymes, thus altering their activities with resultant changes in the metabolism of tumors.

Methods Employed:
In in vitro studies carcinogens labelled with N^{15} would be added to the enzyme solutions. The activities would then be determined, and in an aliquot the enzyme protein would be washed free of unbound carcinogen and tested for N^{15} by the mass spectrograph. In the in vivo studies the rats would be fed the carcinogen and at intervals some rats killed and their livers tested for catheptic and nuclease activities as well as for N^{15} bound to proteins.

Major findings:
This study will be started early in 1955.

Significance to Cancer Research:
Definite changes in catheptic and nuclease activity occur when normal tissues become neoplastic. This study may throw some light on the mechanism of carcinogenic transformation of tissues.

Proposed course of project:
See "Methods employed" above.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. M1-326
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$ 4763	2	1	3	1/3	1/3	2/3	0
FY 1956	$ 4865	2	1	3	1/3	1/3	2/3	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

none

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

none

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis Sec.
SECTION OR SERVICE

LOCATION (IF OTHER THAN BETHESDA)

5. NCI-327
SERIAL NO

6. Mechanism of Carcinogenesis-Metabolism of 2-Acetylaminofluorene and related compounds.
PROJECT TITLE

7. Dr. J. H. Weisburger
PRINCIPAL INVESTIGATOR(S)

8. Dr. E. K. Weisburger
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: Investigation of the mechanism of tumor formation by studying the mode of action of known carcinogenic agents. The problem is attacked in three ways: (1) Study of the in vivo and in vitro metabolism of the strong carcinogen 2-acetylaminofluorene and its interaction with body constituents; (2) Study of the metabolism of related compounds; (3) Determination of the effect of chemical structure of potential synthetic carcinogens on their biological effect.

Methods:
(1) Biochemical techniques involving radioactive tracers (carbon 14) are applied. The tagged atom serves as a convenient tool to analyze tissues or excreta for the presence of metabolites of the labeled compound, for example 2-acetylaminofluorene-9-C^{14}, fed to experimental animals, or obtained by in vitro metabolism. The mixtures of metabolites present are fractionated and identified using paper chromatography, counter-current distribution, fractional crystallizations, vacuum sublimations and other suitable techniques.
(2) Development of new organic synthetic methods for the preparation of compounds required as reference standards for the metabolic studies, and for the determination of biological activity.
(3) Development of analytical methods such as colorimetric, counting, etc. procedures for use in the investigations outlined above.

Major findings:
(1) In vitro metabolism of carcinogens.--Deacetylation of acetylated aromatic amines by tissue homogenates was demonstrated. Studies on the in vitro protein binding of carcinogens and metabolites were initiated and positive results obtained.
(2) In vivo metabolism of 2-acetylaminofluorene (2-AAF).--The following new compounds were shown to be metabolites of 2-AAF: 1-Hydroxy-2-acetylaminofluorene,

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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Continuation sheet

3-hydroxy-2-acetylaminofluorene, 5-hydroxy-2-acetylaminofluorene and the glucuronic acid conjugates of the above named compounds.
(3) Metabolism of 2-C^{14}-monomethylaminofluorene (MAF).--It was shown that riboflavin deficiency altered the metabolism of MAF in the rat. MAF absorption and demethylation was delayed in the deficient animals. On the other hand, panthotenic acid deficiency had no effect on demethylation. Dimethylaminofluorene was not a metabolite of MAF.
(4) Metabolism of 3-Acetylaminofluorene.--3-Aminofluorene was found to be a metabolite, in addition to 2-hydroxy-3-acetylaminofluorene (cf. 1953 annual report).
(5) The following new compound and the required intermediates were synthesized by methods devised in this unit: 2-Acetylamino-5-hydroxyfluorene (7 intermediates). 2-Acetylaminofluorene-9-C^{14} of high specific radioactivity was synthesized in 7 steps from 75 millicuries of radioactive barium carbonate.

Significance to Cancer Research:
The carcinogenic chemical compound 2-acetylaminofluorene used in the study of the mechanism of carcinogenesis not only induces tumors remote from the site of application or ingestion but also gives rise to a variety of histological types and to tumors in many differest tissues. These characteristics of this carcinogen offer hope that it may be one of the most useful tools yet developed for the study of the fundamental factors involved in carcinogenesis, more nearly duplicating spontaneous formation of neoplasms as it is found in rodents and in man. An understanding of the basic mechanisms of tumor formation is essential in arriving at a rational attack on the prevention of the disease.

Proposed course of project:
The present studies will be continued and expanded.

PROJECT REPORT FORM (Cont'd)

10. M-327
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$32,295	3	2	5	2-1/3	2	4-1/3	
FY 1956	$32,298	3	2	5	2-1/3	2	4-1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

15. NCI-327
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. 2-Acetamido-7-methoxyfluorene. J. H. Weisburger and E. K. Weisburger. J. Chem. Soc. 1954, 758-9.

2. Which I^{131} Counting System is Best for Laboratory Use? J. H. Weisburger and H. P. Lipner. Nucleonics 12, no. 5, 21-24 (1954).

3. ortho-Hydroxy Derivatives of the Carcinogen-2-Acetylaminofluorene. E. K. Weisburger and J. H. Weisburger. J. Org. Chem. 19, 964-72 (1954).

4. The Effect of Riboflavine on the Metabolism of 2-Acetylaminofluorene-9-C^{14} in Rats. J. H. Weisburger, E. K. Weisburger and H. P. Morris. J. Natl. Cancer Inst. 15, 37-47 (1954).

5. 2-Hydroxy-3-acetylaminofluorene, a Metabolite of 3-Acetylaminofluorene in the Rat. E. K. Weisburger. J. Am. Chem. Soc. (in press).

6. The Enzymic Deacetylation of the Carcinogen 2-Acetylaminofluorene and Related Compounds. J. H. Weisburger. Biochim. Biophys. Acta (in press).

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Dr. J. Weisburger:

1. Manager of the Chemical Society of Washington (elected for 1954 term).
2. Treasurer of the Junior Scientists' Club, NIH (elected for 1954-5 term).
3. Member of Ad Hoc Committee on Housing, Chemical Society of Washington (appointed).

Dr. E. Weisburger:

1. Member, Program Committee, Chemical Society of Washington (appointed) 1954-1955.
2. Member, Entertainment Committee, Chemical Society of Washington (appointed) 1953-1954.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-528
SERIAL NO

6. Role of Iodine and Goitrogens in the Development of Thyroid Cancer
PROJECT TITLE

7. H. P. Morris and H. J. Lipner (research fellow)
PRINCIPAL INVESTIGATOR(S)

8. B. P. Wagner and J. H. Weisburger
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
The objective of this project is to utilize the functional properties of the thyroid tissue to concentrate and metabolize iodine to elucidate changes which occur during the progress from normal to neoplasia. This technique using I^{131} as an isotopic tracer furnishes a very sensitive method to detect functional changes occurring during the development of thyroid tumors in experimental animals rather than relying on morphological criteria.

Major Findings:
The influence of chronic ingestion of a goitrogen, propylthiouracil (PTU) by mice has been found during the past year to result in either no effect on, or a depression of, the iodide concentrating mechanism (ICM) or T/S ratio. PTU blocks the oxidation of iodide ion (I^-) but does not appear to interfere with the removal of the iodide ion from the blood. A low iodide intake in mice increases ICM while the addition of PTU to the low iodine diet results in depression ICM activity to the same level obtained on a normal iodine diet.

The withdrawal of the goitrogen after a period of chronic feeding resulted in an elevated T/S ratio within 24 hours indicating that the mechanism of thyroid inactivation by PTU in the mouse differs somewhat from that in the rat.

The iodine metabolism of transplantable thyroid gland neoplasms that no longer possess an appreciable ability to metabolize iodine

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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CONTINUATION SHEET

was not influenced by altering the dietary intake of iodine. Some stimulation of the growth of one tumor subline was obtained when the host was fed a low iodine diet containing a goitrogen but simultaneously depressed the hypertrophy of the hosts thyroid gland. The growth of this tumor subline was stimulated by exogenous TSH, but in another tumor subline growth of the tumor was depressed by TSH.

Continued study of the factors causing these divergent results are underway.

The ability of the first and second generation transplants of hypertrophied thyroid tissue to concentrate and metabolize iodine has been studied. The results indicate most of the transplanted tissues have decreased nearly 50% in ability to concentrate iodine, but this loss was not due to transplantation of the tissue to another site per se.

Significance to Cancer Research:
This is a direct approach with the use of a very sensitive technique to determine how the function of normal and cancer cells differ during the gradual course of developing into cancer cells. It is expected that these studies will evolve new understanding of how cancer cells loose many of their functional activities in becoming cancerous.

Proposed Course of Project:
Continued studies of iodine deficiency as a means of inducing transplantable cancer of the thyroid in mice. Development of more adequate diets deficient in iodine will be attempted. Continuation of studies of iodine uptake and metabolism of thyroid tissue in successive transplant generations will be continued. Studies of the activity of iodinating enzymes in the process will be initiated. The work will be greatly slowed unless 1 additional biochemist is recruited.

10. NCI-328
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7597	1	4	5	1/4	1	1-1/4	
FY 1956	$7636	1	4	5	1/4	1	1-1/4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

15. M-328
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

J. H. Weisburger and H. J. Lipner. Which I^{131} Counting System is Best for Laboratory Use. Nucleonics, 12, 21 (1954).

H. P. Morris. Experimental Thyroid Tumors. Brookhaven National Lab. Summer Conference on the Thyroid, June 1954. Brookhaven Conference Report, pp. 192-219, 1954.

H. P. Morris. Nature of the Iodine in Functional Induced Cancer of the Thyroid. Proc. Second Nat. Cancer Conference, pp. 479-481, 1954.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Cytochemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-320
SERIAL NO

6. Development of Unique Manometric and Electrochemical Methods of Measuring Gas Exchange in Cell Metabolism.
PROJECT TITLE

7. Dean Burk and George Hobby
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:

Biochemical, biophysical, and other users of conventional types of manometers have often wished to measure volumes of gas changes with a sensitivity far greater than the commonly obtained order of a cubic millimeter, without having to resort to extensive changes in apparatus, to microscope cathetometers, or to esoteric instrumentation. At the same time, it has been equally desirable to have available electrochemical methods for measuring the still smaller amounts of oxygen involved when oxygen is dissolved in aqueous medium.

Results:

An entirely new system of manometry has been worked out in which amplification of any given, usual sensitivity of the conventional Warburg manometer up to ten to one hundred times can be accomplished in both constant volume and free manometry, without any necessary structural alteration in the manometer, by suitable application of the hydraulic principle that linear displacement of a given volume of fluid in an enclosed tube is a function of the area of the tube at any given point or section. The sensitivity magnification is effected in practice simply by raising the level of the manometric fluid from its usual position in the open arm capillary up into the expanded reservoir section atop the capillary, and inserting into the capillary by means of e.g. a long hypodermic needle, a small stable air bubble whose position at rest is independently stable, in accordance with IXth hydrostatic paradox of Boyle. The linear traverse of the moving boundary bubble in the capillary of small area is greatly magnified compared to the linear traverse of the fluid meniscus in the reservoir of much larger area, and is an inverse function of the ratio of the two respective areas. A new general-purpose hydraulic manometer has

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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Continuation Sheet

been developed in which the capillary arms are of unequal diameters and both are topped by wide-area reservoirs, and this manometer is best adapted to utilizing all of the proposed variations in procedure in not only conventional constant volume manometry and volumetry, but also in the hitherto, very rarely employed "free manometry" (free expansion of confined gas against constant external pressure). Free manometry should now, as a result of the new methodology, become widely useful. The methodology has been climaxed by the development of a very sensitive, rapidly responsive, hydraulic, one-arm "paradox" manometer in which as the amount of confined gas is increased its pressure is decreased (sic). Applications of the new techniques to a wide range of conventional manometer types are possible, including differential and compensation manometers and Cartesian diver techniques.

An electrochemical method has been developed for measuring, with automatic recording, changes of one volume of oxygen in one hundred million volumes of aqueous medium. The measurements were made in rapidly stirred solutions containing a stationary platinum-oxygen electrode (5 x 0.1 mm.) and a large, remote, non-polarizable anode of iron, zinc, or aluminum. Such a galvanic cell, without imposition of external potentials (such as employed in most polaragraphic methods), yielded current values proportional to oxygen up to saturation of the medium with pure oxygen, providing the external resistance in the circuit was below about 500 ohms. Current amplification was obtained with a standard Beckmann millivoltmeter amplifier connected with a Brown recorder.

PROJECT REPORT FORM (Cont'd)

10. M-329
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7728	1	2	3	2/3	2/3	1-1/3	
FY 1956	0	-	-	-				

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

15. NCI-329
SERIAL NO.

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16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

(1) Hydraulic-leverage principles for magnification of sensitivity of gas change in free and fixed-volume manometry. Dean Burk and George Hobby, Science, 120, 640-648, 1954.

(2) Hydraulic amplification of sensitivity in free and fixed volume manometry. George Hobby and Dean Burk, Jour. Cell. Comp. Physiology, December, 1954.

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17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Dean Burk elected : Foreign Member, Max-Planck-Gesellschaft, Germany, December 195

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Cytochemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-330
SERIAL NO

6. Combined actions of anti-cancer agents and hormonal systems that inhibit glucose utilization in cancer metabolism and growth.
PROJECT TITLE

7. Dean Burk and Mark Woods
PRINCIPAL INVESTIGATOR(S)

8. Jehu Hunter
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:

To determine the action and mode of action of anti-cancer agents when used in vitro and in vivo in conjunction with relatively tumor-specific inhibitors of glucose utilization such as components of the hormonal anti-insulin complex.

Methods employed:

Tumor slices are either exposed in vitro to the compound under study, or the compound is administered in vivo and the effects on in vitro metabolism subsequently determined. Methods of metabolic analysis developed in connection with studies of insulin:anti-insulin hormonal systems are employed to evaluate quantitatively and qualitatively the effects and mechanism of action of the agent under test. A series of tumors exhibiting a spectrum of hormonal sensitivities are employed as test systems.

Major findings:

Podophyllotoxin (acetylpodophyllotoxin- -pyridinium chloride) added in vitro to buffered S91 melanoma slices was found to produce immediate (minutes) and marked inhibition (up to 80%) of anaerobic glycolysis, over a mechanism involving steroid-like potentiation of the anti-insulin inhibitor system. Prior exposure of the tumor-bearing mice to stressing temperature (35 deg. C.) accentuated the inhibition of glycolysis by podophyllotoxin. When podophyllotoxin and testosterone were administered simultaneously in vitro at sub. maximal concentrations, more glycolytic inhibition was obtained than with either substance alone. Glycolysis of the insulin-resistant K2 ascites tumor (cell suspensions) was not inhibited by podophyllotoxin in vitro. The inhibitory effects (up to 40%) of podophyllotoxin on respiration of

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

NCI-330

Continuation sheet

S91 melanoma slices were counteracted (85 to 100%) by glucose (0.1 to 0.6%) or glutathione (1 mg. per ml.) and appear to consist of a speeding up of normal oxidative or autolytic deterioration of labile components of the respiratory system. Aerobic glycolysis, however, was inhibited even in the presence of a high level of glucose where respiration was not significantly lowered. The data indicate separate mechanisms of inhibition for glycolysis and respiration.

Triethylenephosphoramide (TEPA)was found to inhibit growth in both S91 melanoma and the amelanotic S91A melanoma, the effect being more pronounced in mice exposed to temperature stress (35 deg. C.). On the other hand thio-TEPA and TEPA, had no effect on anaerobic glycolysis of S91 melanoma slices suggesting a locus of in vivo action other than the glycolytic system per se.

Significance to Cancer Research:

The development of an effective cancer therapy may depend on a multiple approach in which selective inhibition of a specific phase of cellular metabolism (e.g., glycolysis) is employed to enhance vulnerability to simultaneous inhibition of metabolism at another locus (e.g. at some point in the respiratory system). The elucidation of the mechanisms of action of drugs like podophyllotoxin and TEPA should aid in the attainment of the ultimate goal of selective necrotization of the cancer cell in vivo, both in the growing and resting states.

Proposed course of subject:

It is planned to determine the effects of other drugs known to have some oncocidal or oncostatic properties on in vitro cellular metabolism utilizing the technics of metabolic analysis developed in this laboratory, and employing a spectrum of experimental tumors. The combined effects of these compounds, and specific glycolytic inhibitors such as anti-insulin hormones, or compounds having equivalent action, will be investigated in vitro and in vivo.

PROJECT REPORT FORM (Cont'd)

10. AC1-330
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$14,591	2	3	5	1	1	2	
FY 1956	0	-	-	-	-	-	-	

12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for 14, 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Cytochemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-331
SERIAL NO

6. Sub-cellular localization of insulin action in carbohydrate metabolism and growth of tumors.
PROJECT TITLE

7. Paul Hochstein
PRINCIPAL INVESTIGATOR(S)

8. Mark Woods and Dean Burk
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:

The objectives of this research are to study insulin-anti-insulin mechanisms on the sub-cellular level and to relate these mechanisms to the regulation of carbohydrate metabolism and growth in normal and malignant tissues *in vivo*.

Methods:

Tumors are available which differ in the extent to which their glucose metabolism is sensitive to insulin. Cells of such varying tumors are disrupted by mechanical means, and the effects of insulin and endogenous and exogenous insulin-opposers on the glycolysis of sub-cellular components are studied by manometric techniques.

Major Findings:

Homogenates were prepared from mouse melanoma S91 grown in dba mice in which the rate of anaerobic glucose utilization ($Q^{N_2}_{CO_2}$) was nearly linear for periods of 20-30 minutes. Exposure of melanoma-bearing mice to elevated temperatures (ca. 35°C., 6-24 hrs.) resulted in a marked diminution and rapid decay in the rate of anerobic glycolysis of tumor homogenates. The addition of hexose diphosphate to these homogenates prevented the decay in glycolysis, and the glycolysis values approached those for tumor homogenates prepared from animals which had not been exposed to elevated temperatures. The rate of glycolysis in tumor homogenates from animals not exposed to high temperatures was approximately the same in the presence of glucose or hexose diphosphate.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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Continuation Sheet

In certain experiments the addition of approximately 1 unit of crystalline zinc-insulin per ml. of tumor homogenate from heat-treated animals resulted in increases of 10-60% in the rate of anerobic glycolysis, in harmony with recent work had shown that insulin-reversible lowering of glycolysis in tissue slices of S91 melanoma from heat-treated mice is associated with an increase in anti-insulin hormones in the tumor. The action of anti-insulin hormones appears to be greatly accentuated in the cell-free systems as compared with the slice. The current findings indicate that insulin-anti-insulin mechanisms can operate in sub-cellular systems, and in particular in the hexokinase reaction.

Proposed:

During the next year it is proposed to continue studies which will more precisely define the interaction of insulin with various hexokinase inhibitors or insulin-opposers. Available purified hormonal preparations will be utilized as well as fractions obtained from tumors, endocrine glands or other normal tissues. It is further proposed to investigate the possible particulate binding of insulin-reversible hexokinase inhibitors.

PROJECT REPORT FORM (Cont'd)

10. ML-331
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$15945	2	2	4	1-1/3	2/3	2	0
FY 1956	$15,912	2	2	4	1-1/3	2/3	2	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for 14, 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Cytochemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-332
SERIAL NO

6. Differential Effects of Temperature Stress on the Growth of Certain Transplanted Tumors.
PROJECT TITLE

7. Jehu Hunter
PRINCIPAL INVESTIGATOR(S)

8. Mark Woods and Dean Burk
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION**

Objective:
To determine the effect of temperature stress on the growth of transplanted tumors.

Methods:
Tumors are available which differ in their growth response to temperature stress, and, similarly, in their sensitivity to temperature-induced, insulin-reversible lowering of glycolysis over host mechanisms. Tissue from such varying tumors is inoculated into host animals and the growth of these tumors is determined by periodic caliper measurements in 3 dimensions. Growth and metabolic data from similar tumor types are correlated.

Major Findings:
A differential growth response was observed in the S91 melanoma, S91A amelanotic melanoma and the Krebs 2 carcinoma when dba mice bearing these tumors were kept at 35° and 25° C. Growth of the S91 melanoma was markedly and immediately inhibited when the host was kept at 35°C., but exposure to environmental 25°C. reversed the inhibition. Inhibition of growth in the S91A amelanotic melanoma occurred at 35° C., but, in contrast to the S91, only after a week or so of exposure and was of a lower order of magnitude. The Krebs 2 carcinoma in solid form grew well at 35°C., but the mortality rate of the hosts was higher than at 25°C. These effects reflect in part, a differential response of these tumors to host endocrine changes in response to a stressing agent, namely, elevated temperature, in line with earlier *in vitro* studies showing that the S91 melanoma, S91A amelanotic melanoma,

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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and the Krebs 2 carcinoma differ greatly in the same order with respect to their sensitivity to temperature-induced, insulin-reversible lowering of glycolysis over host mechanisms.

Under certain conditions S91 melanomas in mice kept at 35°C. resumed growth after several weeks of exposure. Autopsy of such animals revealed that the tumors were macroscopically lighter in color than tumors inhibited by stressing temperature and that grossly amelanotic areas were evident. Tissue from these lighter areas transplanted into other dba males grew as well at 35°C., as did implants of S91A amelanotic melanoma, and this line of derivative tumors has been continued. The in vitro pattern of metabolism in these relatively amelanotic S91 tumors, obtained by growth at 35°C., resembled the metabolic pattern for the earlier derived S91A amelanotic melanoma. These observations indicate that different tumors react differently to endocrine changes in the host resulting from the stressing effects of high temperature. They also suggest that the appearance of amelanotic areas in S91 tumors at 35°C. might be the result of some form of hereditary variation involving a modified response (lowered sensitivity) to the anti-insulin hormonal system.

PROJECT REPORT FORM (Cont'd)

10. [illegible]-332
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7,973	2	1	3	2/3	1/3	1	
FY 1956	0	-	-	-	-	-	-	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

No entries for 15, 16, and 17

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Cytochemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-333
SERIAL NO

6. Steroidal inhibitors in oxidation and glycolytic enzyme systems in tumors
PROJECT TITLE

7. Kent Wight
PRINCIPAL INVESTIGATOR(S)

8. Dean Burk
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Methods and objectives:

Electrometric methods are combined with manometry for the study of biochemical reactions such as changes in oxygen, oxidation-reduction potential, carbon dioxide, and pH (fixed acid).

Results:

(a) Diethylstilbestrol at 10-2M-to 10-4M inhibited oxygen consumption 30-95%, with succinate and cytochrome C as the substrates, and with both tissue slices and homogenates. The following tissues from mice were used: heart, brain, liver, Harding-Passey and S91 melanomas, and the C_3HBA adenocarcinoma. The diethylstilbestrol was more effective when added to the tissue some period of time (30'-45') before the succinate and cytochrome C. That this inhibitory action of stilbestrol was directed at cytochrome oxidase was shown by the fact that the oxygen consumption was inhibited with the substrate paraphenylenediamine (0.02M), in agreement with reports in the literature indicating that the action is primarily on the cytochrome oxidase because when brilliant cresyl blue was substituted for cytochrome C, little or no inhibition of gas consumption in the presence of succinate ap occurred. Testosterone (2x10-4M and 10-4M) and progesterone (10-4M) reversed the inhibitory action of stilbestrol (5x10-4M) on the succinoxidase system.

(b) Diethylstilbestrol·K_2SO_4 inhibited the aerobic and anaerobic glycolysis of a number of tumors at the slice, homogenate and subcellular levels.. The tissues studied were K2 ascites (solid and liquid) tumor, C_3HBA adenocarcinoma and S91 melanoma.

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

PROJECT REPORT FORM (Cont'd)

10. AC1-333
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$15,945—	2	2	4	1 1/3	2/3	2	
FY 1956	0	-	-	-	-	-	-	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

15. ACI-333
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Wight, Kent and Burk, Dean. Oxidation-reduction Potential and pH Changes in Manometric Vessels. Method for Continuous Recording. Anal. Chem. 26: 481-84 (1954).

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Cytochemistry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-334
SERIAL NO

6. The occurrence and function of a stress-modifiable insulin:anti-insulin hormonal complex regulating glucose utilization in cancer metabolism and growth.
PROJECT TITLE

7. Mark Woods and Dean Burk
PRINCIPAL INVESTIGATOR(S)

8. Jehu Hunter and Paul Hochstein
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives:
To develop *in vitro* metabolic procedures for defining qualitatively and quantitatively the operation of a stress-modifiable insulin:anti-insulin hormonal mechanism that regulates cellular glucose utilization, and to determine its importance in controlling cancer metabolism and growth.

Methods employed:
Tumor-bearing mice are exposed to normal (20 to 25 deg. C.) or stressing (35 to 40 deg. C.)environmental temperatures, and the effects on tumor metabolism and growth determined. *In vitro* measurements of anaerobic glucose uptake and glycolysis ($Q_{CO_2}^{N_2}$), in the presence and absence of insulin and certain steroids, are expressed as rate-time curves at successive cycles of temperatures of incubation (e.g., 20° to 40° to 20° to 40°, or 20° to 10° to 40°). Metabolic findings in vitro are correlated with in vivo effects of temperature stress on tumor survival and growth. Comparative metabolic studies with human tumors are made when feasible.

Major findings:
It has been shown that a stress-modifiable insulin:anti-insulin hormonal system exerts a profound control over the metabolism and growth of certain mouse tumors (melanomas), and that progressive anaplasia is associated with loss of sensitivity (of both growth and metabolism) to the hormonal factors involved. From the form of the rate-time curves for glycolysis as modified by certain exogenous factors it was possible to predict with considerable accuracy the ability of different types of tumors (S91, S91A, K2) to grow

(PLEASE ADD SHEETS AS NECESSARY FOR CONTINUATION)

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Continuation Sheet

in mice undergoing temperature stress. Tumor sensitivity to the stress-accentuated endogenous inhibitor mechanism which regulates the rate of glycolysis is revealed by the extent and type of modification occurring in the glycolysis—time curve as a result of changes in the *in vitro* incubation temperature (e.g., 20° to 40° C. and *vice versa*), changes in concentration of exogenous glucose, insulin, and steroid (e. g., testosterone *but not cholesterol*). Changes in these factors result in a gradual, reversible, and characteristic repoising of the glycolytic rate in hormone-sensitive tumors. On this basis it could be shown that the glucose metabolism of the S91 melanoma is much more under control of the stress-modifiable insulin: anti-insulin hormonal system than in the more anaplastic amelanotic derivative S91A tumor. The K2 carcinoma on the same basis could be classed as resistant to this hormonal system; a conclusion confirmed by the ability of the tumor to grow at almost normal rate in temperature-stressed host mice. Glucose metabolism of the Harding-Passey mouse melanoma, and human melanoma appeared to be strongly under the influence of insulin:anti-insulin hormonal regulation although qualitative and quantitative differences peculiar to these tumors occurred.

The data show that a hormone-responsive tumor, such as the S91 melanoma, can be used as a sensitive metabolic bioindicator of changes or abnormalities in host endocrine balance.

Severe alloxan diabetes (blood sugar 400 to 600 mg per cent) was found to have much less effect on S91 melanoma glycolysis than even short periods (12 hours) of temperature stress.

Significance to Cancer Research:

The metabolic data obtained by these *in vitro* methods supplies a new basis for evaluationg hormonal sensitivities and growth potentialities of tumors. The data obtained give a better understanding of hormonal regulation of metabolism and growth in cancer. They suggest specific approaches to the problem of cancer therapy since the malignant cell is peculiarly geared to a glucose metabolism and relatively specific (acting more on the cancer than on the normal cell) inhibition of anti-insulin factors of this process may create increased sensitivities to drugs or other hormones having an effect on e.g., cellular respiration. It is hoped that a number of spontaneous tumors will prove to be specially vulnerable to this type of attack. The metabolic procedures developed should also be particularly useful in evaluating the mechanism of action of certain anti-cancer drugs.

Proposed Course of Project:

Results secured to date indicate the desirability of extending these new methods of metabolic hormonal analysis to a wider spectrum of tumors; especially to "spontaneous" (human or animal), or recently induced, cancers. Isolation and concentration of the pituitary anti-insulin lipoprotein (described by Krahl, Cori, Bornstein, *et al* in non-cancerous animals), and its *in vivo* testing in conjunction with active anti-insulin steroids is strongly indicated. The combined action (*in vitro* and *in vivo*) of anti-insulin factors which inhibit glucose utilization with compounds showing some selective inhibition of respiration will be studied with special emphasis on

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induction of tumor necrosis. The possible further application of stress as a means of accentuating the whole anti-insulin syndrome in tumors will be studied.

PROJECT REPORT FORM (Cont'd)

10. NCI-334
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$14571	2	3	5	1	1	2	
FY 1956	0	-	-	-	-	-	-	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

PROJECT REPORT FORM (Cont'd)

15. NCI-324
SERIAL NO.

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

a. Woods, Mark, Hunter, Jehu and Burk, Dean. Effects of insulin on aerobic metabolism of mouse brain. Federation Proceedings 13: 324, 1954.

b. Burk, Dean, Hunter, Jehu, and Woods, Mark. Insulin-sex hormone antagonism in Mouse Melanoma and Glycolysis. Proceed. of the Amer. Assoc. for Cancer Res. 1: 7, 1954.

c. Woods, Mark. Polyvinylpyrrolidone (PVP) as adjunct in centrifugal separation and enzymic assay of subcellular components. Proc. of the Soc. for Exp. Biol. and Med. 87: 71-73, 1954.

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

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